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**‘Social Competence and Executive Function in  
Children treated with Bone Marrow Transplant  
(BMT) for Congenital Immunodeficiency’**

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## Overview

Until the mid 1960's, chronic illnesses, such as leukaemia, and congenital immunodeficiency were almost always fatal. The advent of paediatric bone marrow transplant (BMT), however, has resulted in an increasing number of long-term survivors. Concurrent with these medical advances, and based on extrapolation from studies of children treated conventionally for cancer, research has begun to investigate long term cognitive and psychosocial outcome in this cohort of children. Findings are inconsistent and vary from minimal evidence of later difficulties to indications of severe cognitive and psychosocial problems.

**Part one** of this thesis seeks to critically and systematically examine the current evidence base regarding long-term cognitive and psychosocial outcome for children treated with BMT. An attempt is made to identify correlates of outcome and populations of children that may be at particular risk for developing later difficulties. Methodological limitations of the studies published to date are explored and suggestions made for future research.

**Part two** uses a homogenous sample of thirty one children treated with BMT for congenital immunodeficiency, and a matched control group, to examine potential mechanisms underlying the difficulties with social functioning, previously identified in this cohort of children. Both cognitive processes (executive function ability) and non-social attributes of physical appearance and athletic ability were explored, with findings lending most support for the latter.

**Part three** seeks to briefly evaluate the current state of paediatric BMT research and critically reflect upon the contribution made by the current thesis. It also attempts to assimilate the knowledge gained from both the current study and previous research to develop a theoretical framework that might be used to guide clinical assessment and intervention for this cohort of children.

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## **‘Part 1: Literature Review’**

**‘What Effect does Paediatric Bone Marrow Transplant  
(BMT) have on Cognitive and Psychosocial  
Development?’**

## **Abstract**

Significant progress in medical techniques over the past 40 years has resulted in the increased survival rate for chronically ill children and adolescents treated with Bone Marrow Transplant (BMT). Concurrent with these medical advances, research has emerged investigating the long-term psychological outcome for paediatric BMT survivors. From these studies it is possible to learn a great deal about the cognitive and psychosocial functioning of children and adolescents treated with BMT and their families. The field has progressed from descriptive studies of adjustment to more explanatory research. It is an apt time for a review of the progress made, the current state of research in this field and the perspectives on future directions.

## **Introduction**

Bone Marrow Transplantation was introduced in the early 1960's. It has rapidly developed from an experimental procedure to an established treatment offered to chronically ill children who have haematological, oncological, or metabolic diseases. Children are also offered BMT if they have failed conventional treatment protocols due to disease relapse. Whilst still considered an aggressive, life threatening medical procedure, the therapeutic success of paediatric BMT, in terms of increased survival rates, is improving.

BMT generally requires hospitalisation of 6-10 weeks. During this time the child is restricted to their room and allowed only limited contact with family members. Treatment begins with intensive chemotherapy (with or without radiation) over a period of approximately 10 days to destroy tumour cells and/or eradicate existing bone marrow and immune function. Following this therapy, the patient is 'rescued' with an infusion of healthy marrow stem cells from a matched donor (an allogenic transplant) or of bone marrow taken from the recipient and treated before return (an autologous transplant). For a minimum of 2-4 weeks, patients have no functioning bone marrow. Numerous toxic side effects are common, including nausea, pain, infections, hair loss, mucositis (deterioration of the mucous membranes in the mouth and gastrointestinal tract) and skin breakdown.

The potentially fatal complications of BMT include veno-occlusive disease of the liver, pulmonary fibrosis, septicaemia, and intracranial bleeding. Allogenic BMT can also result in graft versus host disease (GVHD), a complication in which the donor's marrow mounts an immunological response to the recipient's cells. This results in similar symptoms to autoimmune diseases like arthritis or scleroderma as well as liver disease.

During treatment BMT patients are exposed to a multitude of medications that may affect cognitive function or affective state. Chemotherapeutic conditioning agents have been associated with acute Central Nervous System (CNS) changes including delirium and



transient encephalopathy, and the association of bulsophan with the development of seizures is so well established that prophylactic use of anticonvulsants (with their own CNS effects) is standard care. The agents commonly used for prophylaxis and/or treatment of GVHD also have well-known associations with CNS effects: corticosteroids associated with affective disturbance and cyclosporine associated tremor, seizures, visual disturbances and hallucinations (Phipps & Barclay, 1996).

Bone Marrow Transplantation is known to cause short-term psychological morbidity. Acute stress responses in children and their parents to the prolonged hospitalisation and severe medical symptoms are well documented (see Powers et al., 1996 for a review). The BMT process can also cause disruptions in family functioning (Phipps & Barclay, 1996). There is often extended separation of family members, particularly when the transplant occurs in a setting far removed from the family's home community.

Following discharge from hospital, the child remains subject to a high level of isolation. Contact with non family members is restricted due to protracted poor immune system functioning. School attendance is often not allowed for 3-9 months and may result in an entire academic year being missed. The child may also experience occasional set-backs, requiring hospital re-admission. As their immune functioning improves and restrictive precautions are reduced, the child must then adjust to reintegration to school and social interactions.

Until recently, the main emphasis was to evaluate the success of BMT by survival rates and degree of immunological improvement. However, over recent years there has been increasing concern that a significant number of transplanted children may later experience mental health problems, especially cognitive and behavioural difficulties. This concern has been based largely on extrapolation from studies of acute lymphoblastic leukemia survivors, which demonstrated that CNS preventative therapy, with and without cranial

irradiation, is associated with transient as well as permanent neurologic disturbances, including neuropsychological deficits (see Bartlett & Moore, 2005 for a review). In addition, extended periods of isolation necessitated by the BMT procedure may put these children at further risk for cognitive and psychosocial developmental delays. This prompted a shift in research away from just focusing on the acute phase of transplant to investigating the long-term cognitive and psychosocial functioning of children treated with BMT. Such information is crucial for determining the relative risks and benefits of BMT in comparison to conventional treatments, particularly for the purposes of informed consent. Families can consider long-term psychological issues, not just survival rates. Documenting BMT associated toxicities can also influence the planning of future conditioning regimens. In addition, it can help identify groups of children who are at high risk for cognitive and/or psychosocial difficulties, who can then be targeted for early intervention. Furthermore, this information is useful for teachers when these children return to school as it can help to develop appropriate expectations for the child's performance.

### **Review of studies investigating the long term cognitive and psychosocial functioning of children treated with BMT**

Given that BMT has only recently become established as a widely used treatment for a range of childhood disorders, there are a limited number of studies examining long-term outcomes. This review includes 24 published studies that have investigated the cognitive and/or psychosocial outcome for children treated with BMT. Studies investigating the Quality of Life (QOL) of paediatric BMT survivors were not included. Tsimiscalis et al. (2005) recently conducted a systematic review of the 10 studies to date that have investigated the QOL of children following bone marrow transplant. They were unable to draw reliable conclusions due to significant methodological problems, primarily resulting from a lack of

consensus regarding the QOL definition between studies. Thus, this review focuses solely on cognitive and psychosocial (social, behavioural, emotional) aspects of functioning. For the purposes of the review the cognitive and psychosocial sections are separated. However, these two areas should be considered as intertwining aspects of the child's total functioning (Patenaude & Kupst, 2005).

The studies in both sections were reviewed in order to answer the following questions: (1) What are the methodological characteristics of studies exploring the long-term cognitive and psychosocial outcomes for children treated with BMT?; (2) What are the long term cognitive and psychosocial outcomes for children treated with BMT; (3) Are there any particular areas of cognition/domains of psychosocial functioning that are affected by the BMT process; (4) Can correlates of cognitive and psychosocial functioning following BMT be identified; (5) Bringing the two sections together, are there particular populations of children that are at increased risk of developing cognitive and /or psychosocial difficulties following BMT; (6) What are the methodological limitations of these studies; and (7) What are the directions for future research?

#### *Search strategy for identification of studies*

Studies for inclusion in the review were accessed primarily through a search of Psychinfo, Medline, CANCELIT, EMBASE, Google Scholar and the journal 'Bone Marrow Transplantation'. The search terms included the following key words: 'BMT', 'child', 'children', 'childhood', 'paediatric', 'cognitive', 'neurocognitive', 'neuropsychological', 'psychosocial', 'social', 'emotional', 'behavioural' and 'outcome'. The date of the last search attempt was March 2008. Reference lists from all identified papers were examined and a hand search for other appropriate studies conducted. No attempt was made to locate unpublished material.

## **Section1: Cognitive Outcome**

### *Methodological characteristics of cognitive outcome studies*

Table 1 provides an outline of the 17 studies reviewed. All studies recruited only childhood BMT recipients, with the exception of Parth et al., 1989, who included adults within their sample.

The number of participants at post-BMT evaluations varied considerably from four (Kaleita et al., 1989) to 153 (Kupst et al., 2002) and involved a total of 847 children, adolescents and adults. Most of the studies included children presenting with a range of diagnoses, in particular varying types of haematological malignancies, making it difficult to directly compare and contrast findings. Two more recent studies used homogenous diagnostic samples of children treated only for extracranial tumours (Notteghem et al., 2003) and congenital immunodeficiencies (Titman et al., in press). These studies are useful in allowing for identification of illness specific factors related to long term outcome. Most children presented with different BMT types. Two studies included only autologous (Arvidson et al., 1999; Notteghem et al., 2003), five studies included only allogenic (Chou et al., 1996; Halberg et al., 1990; Kaleita et al., 1989; Smedler et al 1990; Titman et al., in press) whilst others included both autologous and allogenic (Kupst., 2002; Phipps., 1995, 2000; Simms et al., 1998). Six studies did not specify type of BMT (Cool, 1996; Kramer et al., 1992, 1997; McGuire et al., 1991; Parth et al., 1989; Smedler et al., 1995).

Age at BMT ranged from two months to 19.5 years (both Notteghem et al., 2003), with age at cognitive testing ranging from 3.5 years (Titman et al., in press) to 44 years (Parth et al., 1989). This considerable variation in methodology will limit ability to draw reliable conclusions across studies.

There were considerable differences in study eligibility criteria, reflecting further variations in methodological quality between studies. Four studies required participants to have been in complete remission for at least one year (Arvidson et al., 1999; Notteghem et al., 2003; Smedler et al., 1995; Titman et al., in press). To study the effects of treatment variables, four studies included /excluded children based on the type of conditioning treatment they had received: two excluded those who had not received Total Body Irradiation (TBI) (Chou et al., 1996; Halberg et al., 1990); one excluded those who had received TBI or Cranial Radiation Therapy (CRT) (Notteghem et al., 2003); another excluded those who had previously received CRT (Simms et al., 1998). To investigate the effect of young age on outcome, two studies only included children treated with BMT at three years or younger (Kaleita et al., 1989; Smedler et al., 1995). Three studies excluded children if they underwent BMT for brain tumour (Kramer et al 1997; Phipps et al., 1995, 2000) as illness and treatment factors in this group of children varies considerably from that of others treated with BMT. Given that the cognitive tests used were predominantly standardised using samples of English speaking children, two studies excluded children for whom English was not the primary language (Phipps et al; 1995, 2000).

Most studies employed a prospective longitudinal design to assess change over time (Arvidson et al., 1999; Chou et al., 1996; Cool, 1996; Kramer et al., 1992, 1997; Kupst et al., 2002; Parth et al., 1989; Phipps et al., 1995; 2000; Simms et al., 1998). These studies collected data ranging from 50 days (Parth et al., 1989) to seven years post BMT (Arvidson et al., 1999). Five studies collected data on two or more occasions post BMT (Chou et al., 1996; Kramer et al., 1997; Kupst et al., 2002; Parth et al., 1989; Phipps et al., 2000). To control for social and demographic factors, two studies employed a comparison group of siblings/family members (Parth et al., 1989) and children facing a similar life threatening disease but not undergoing BMT (Cool, 1996). Due to limited sample sizes, two studies employed a multiple case study design, allowing for detailed examination of individual

cognitive responses across time, post BMT (Kaleita et al., 1989; Smedler et al., 1995). Both administered tests on one to three occasions, one to seven years post BMT.

Five studies used cross sectional designs permitting larger sample sizes but reducing ability to make causal inferences (Halberg et al., 1990; McGuire et al., 1991; Notteghem et al., 2003; Smedler et al., 1990; Titman et al., in press). Participants were assessed from seven months (Halberg et al., 1990) to 25 years (Titman et al., in press) post BMT. Three studies employed sibling comparison groups (McGuire et al., 1990; Smedler et al., 1990; Titman et al., in press).

Most studies used standardised measures of cognitive functioning. These included the Wechsler Scales of Intelligence (Wechsler, 1974; 1981; 1989; 1991; 1999; 2004); the Bayley Scales of Infant Development (Bayley, 1969) ; The Stanford Binet Intelligence Scales (Thorndike et al., 1986) and the Griffiths Mental Development Scales (Griffiths, 1970; 1996). These tests provide reliable and valid measures of cognitive functioning and are widely used in both research and clinical settings. One study used a standardised micro-computer based neuropsychological battery (Parth et al., 1989) and one study did not specify their assessment instruments (Halberg et al., 1990).

Some studies included additional, standardised measures to assess specific areas of neuropsychological functioning. These included tests of academic achievement (Cool, 1996; Kramer et al., 1992, 1997; McGuire et al., 1990; Notteghem et al., 2003; Phipps et al., 1995, 2000); motor functioning (Arvidson et al., 1999; Cool, 1996; Kaleita et al., 1989; Kramer et al., 1992, 1997; Notteghem et al., 2003; Parth et al., 1989; Phipps et al., 1995, 2000; Simms et al., 1998; Smedler et al., 1990, 1995); memory (Arvidson et al., 1999; Notteghem et al., 2003; Phipps et al., 1995, 2000; Simms et al., 1998;); processing speed (Phipps et al., 1995, 2000) and attention (Arvidson et al., 1999; Phipps., 1995, 2000).

Table 1 Chronological summary of cognitive outcome in paediatric BMT survivors

Study	sample	Design and measures	Age at BMT; Age at Assessment	Results: Cognitive outcome	Factors associated with cognitive outcome	Factors not associated with cognitive outcome	comments
Kaleita et al. (1989)	N=4 ALL: N=2 SAA: N=2	Prospective multiple case study. Gesell Development Assessment Schedules; Stanford Binet Intelligence Scale; WISC- R administered pre BMT and 2-6 years post-BMT	36 weeks-24 months at BMT	Normal development of intelligence, language, perception and motor co- ordination. No change over time	-	-	First cases reported; 2 infants received TBI, 2 did not.
Parth et al. (1989)	N=20 Hematological malignancies; SAA	Prospective; standardized microcomputer-based neuropsychological battery, administered pre BMT, day+50; day +100 and 1 year post BMT. Control group of BMT donors(N=9)	Age range: 8-44 years	No decrement in performance over time; some deficits in comparison to controls, most notably associative memory, perceptual speed and logical reasoning	-	-	Only 11 patients, 3 control participants at 1 year F-up.
Halberg et al. (1990)	N=6 SCID: N=4 CHS: N=1 WAS: N=1	Cross-sectional neuropsychological assessment (not specified) at 7-72 months post BMT	Age range: 3-56 months	Cognitive testing on the oldest child (6.3 years old), 6 years post BMT, revealed normal IQ. Evaluations on the younger children, age 9-36 months demonstrated evidence of motor co- ordination and language skills development	-	-	Only 6 patients. All received TBI.

Study	sample	Design and measures	Age at BMT; Age at Assessment	Results: Cognitive outcome	Factors associated with cognitive outcome	Factors not associated with cognitive outcome	comments
Smedler et al. (1990)	N=32 Leukaemia: N=25 SAA: N= 6 SCID: N=1	Cross sectional. Swedish adaptation of Griffiths Mental Development Scale; WISC-R; WAIS - R administered 1-6 years post BMT Sibling control group: (N=32)	1.0-17.2 years at BMT 4.0-23.6 years at assessment	No cognitive deficits in children 12 yr+ at time of BMT. Cognitive impairment present among the 4 youngest (<3 yr) leukaemia patients who received TBI. Motor skills (perceptual and fine motor speed) particularly affected compared to donors	Age Combination of TBI and chemotherapy	-	All received TBI. Motor delays in younger children difficult to interpret as overall developmental assessment not administered to youngest children
McGuire et al. (1991)	N=178 Hematological malignancies	Cross-sectional; compared 110 patients assessed pre-BMT to 68 patients assessed 1-12 yr post BMT on WISC-R; WAIS-R; WRAT-R Sibling control group (N=38)	Age range 6-18 years (median 11 yr) at BMT	No differences between the pre and LT follow up groups on any measures	Age at irradiation; Amount of irradiation Years since first irradiation	Gender Source of irradiation (TBI or cranial irradiation)	Published only as an abstract
Kramer et al. (1992)	N=22 SCID: N=9 Neuroblastoma: N=6 ALL: N=6 Thalassemia: N=1	Prospective; Bayley Scales of Infant Development; Stanford Binet Intelligence Scale; WISC-R administered pre BMT and 1 year post BMT	Mean age: 31.1 months at BMT; 45.8 months at assessment	No decrements in cognitive functioning 1 year post BMT. But examination of individual test scores indicated that 25% (N=10) experienced a 10+ point change in IQ with the majority (7) moving in a downward direction. 3 had decrements of 20+ points	-	Dose of cranial irradiation Age at administration of irradiation diagnosis	Very young sample, hence did not assess specific areas of cognition. TBI less than 1200cGy.



Study	sample	Design and measures	Age at BMT; Age at Assessment	Results: Cognitive outcome	Factors associated with cognitive outcome	Factors not associated with cognitive outcome	comments
Smedler et al. (1995)	N=10 ALL: N=7 Neuroblastom: N=1 SAA:N=3	Multiple case study; Griffiths Mental Development Scale-II; administered on one to three occasions at 2 year intervals, 1.2-7.3 years post BMT	Mean: 1.0-3.6 at BMT	General developmental delay in irradiated patients: 4/6 showed negative developmental trend with developmental lag more apparent over time. Problems with motor speed, sustained attention, strategy and planning. Pronounced LD in 3/6 irradiated patients	Irradiation  Age	Diagnosis of SAA (non irradiated)	All treated with BMT at <3 years.
Phipps et al. (1995)	N=25 ALL: N=4 ANLL: N=9 Other leukaemia: N=6 Other: N=6	Prospective longitudinal; WPPSI-R; WISC-R/III; WAIS-R; Bayley Scales of Infant Development; WRAT administered pre BMT and 6-12 months post BMT	At assessment: <6 = 4 6-12 = 8 12-18 = 9 >18 = 4	No decrements noted on any measure; only changes seen involved improvement and may be related to practice effects or pre BMT difficulties in concentration. Post hoc; only 5/25 patients showed a decline in FSIQ post BMT, 3 who received TBI and 2 who did not.	-	-	-
Chou et al. (1996)	N=73 ALL: N=58 Congenital immune deficiency: N=15	Prospective longitudinal; Bayley Scales of Infant Development; Stanford Binet Intelligence Scale- IV; WISC-R administered to 42 patients pre-BMT. Follow up assessments administered to all patients 1 and 3 years post BMT	Mean age at BMT: Leukaemia: 8.4 years Immunodeficiency: 1.2 years	Significant IQ reduction between baseline and 1 yr F- up with some recovery at the 3 yr F-up	TBI	Age at BMT  Gender	All received TBI in conditioning

Study	sample	Design and measures	Age at BMT; Age at Assessment	Results: Cognitive outcome	Factors associated with cognitive outcome	Factors not associated with cognitive outcome	comments
Cool. (1996)	N=76 ALL ANLL CML SAA	5 studies including descriptive, prospective, correlational and comparison designs. Weschler Scales of Intelligence; WRAT administered up to 4 years post BMT. Matched control group	6-19 years at assessment (pre BMT)	At pre BMT evaluations, children who had received prior cranial irradiation showed signs of declining IQ scores and below average academic achievement. By 4 years post BMT evidence of declining IQ, achievement, memory and fine motor skills	Young age at diagnosis  CRT prior to BMT	-	-
Kramer et al. (1997)	Initial cohort: N=142 N=65 1 year F-up N=26 3 year F-up SCID: N=16;11 MHD: N=26;9 NMHD: N=9;1 Other: 1;0	Prospective longitudinal; Bayley Scales of Infant Development; Stanford Binet Intelligence Scale – IV; WISC-R/III; WRAT administered pre, 1 and 3 years post BMT	Age at BMT: 3.7 years (SD: 47.5; range: 0.1-17.5)	Sig. drop in IQ between baseline and 1 year follow up. Relative stability of IQ scores between 1 and 3 year follow up points. Levels of academic achievement sig. below population mean	-	Age at BMT  CNS treatment	Majority less than 3 years of age at the time of BMT
Simms et al. (1998)	N=51 at 1 yr F-up AML/CML: N=20 ALL: N=9 Neuroblastoma: N=7 SAA: N=2 Other: N=13	Prospective longitudinal; compared those who received chemotherapy and TBI with those who received chemotherapy only. Bayley Scales of Infant Development; WPPSI-R; WISC-R/III; WRAT administered pre and 1 year post BMT	Mean age pre BMT: Chemo+TBI: 81.43 months (SD: 61.63); Range: 9-274.20  Chemo only: 96.17 months (SD: 57.55); Range: 15.63-202.33	No decrements on any measure of cognitive functioning 1 year post BMT. No differences between children who received chemotherapy and TBI and those who received just chemotherapy.	Pre-BMT functioning	Gender  Age  Chemotherapy	Test scores for 3 of 4 surviving children who underwent BMT at less than 3 years of age decreased at 1 year post BMT.

Study	sample	Design and measures	Age at BMT; Age at Assessment	Results: Cognitive outcome	Factors associated with cognitive outcome	Factors not associated with cognitive outcome	comments
Arvidson et al. (1999)	N=26  ALL: N=18 AML: N=4 Lymphoma: N=4	Prospective longitudinal; WISC-R; WAIS-R administered 2-7 years post BMT; additional cross-sectional study using neuropsychological tests of executive functions and visuo-and sensory-motor capacity.	Mean age at BMT: 9.8 years  Mean age at evaluation: 16.1 years	General intelligence within the normal range and mainly unaffected over time. Below average performance in specific neuropsychological tests of executive function (attention, strategies and memory)	Young age at diagnosis  Long time since BMT  High intensity of treatment	-	Only tested children who had undergone autologous BMT.
Phipps et al. (2000)	N=102 at 1 year F-up; 54 at 3 year F-up  ALL: N=16;11 AML: N=32;20 CML: N=21;14 Other leukaemia: N=8;1 other: 25;8	Prospective longitudinal; Bayley Scales of Infant Development; WPPSI-R; WISC-R/III; WAIS-R; WRAT-R/III administered pre, 1 and 3 years post BMT.	Age at BMT: 1 year follow up group: 10.41; SD 5.8)  3 year follow up group: 10.83 (SD 5.7)	No sig. changes on global measures of intelligence and academic achievement at 1 or 3 years post BMT. But sig. decline in cognitive functioning over time in children less than 3 years of age at BMT	Age at BMT	Gender Diagnosis Type of transplant Use of TBI Presence of acute or chronic GVHD Prior CNS therapy	Findings suggest executive function skills are most affected post BMT.
Kupst et al. (2002)	N=153, 1 year post BMT (initial cohort 377) N=74, 2 years post BMT ALL: N=62 ANLL: N=22 SAA: N=22 CML: N=13 Other: N=34	Prospective longitudinal; Bayley Scales of Infant Development; WPPSI-R; McCarthy Scales of Children's Abilities; WISC-R/III; WAIS administered pre, 1 and 2 years post BMT	Mean age at BMT: 9.6 years (SD 5.3 years)	Cognitive functioning within normal range with no sig. change over time. Only area of cognition that differed from normative data was mental arithmetic.	SES	Age at BMT  Previous chemotherapy  TBI  Acute or chronic GVHD	No consistent pattern of cognitive functioning found for children under 3 years at BMT.

Study	sample	Design and measures	Age at BMT; Age at Assessment	Results: Cognitive outcome	Factors associated with cognitive outcome	Factors not associated with cognitive outcome	comments
Notteghem et al. (2003)	N=76 (initial cohort 142) Neuroblastoma: N=46 Ewings Sarcoma: N=10 Other tumour types: N=20	Cross sectional; French adaptations of WPPSI-R; WISC-III; WAIS-III administered a median 9.1 years post BMT	Mean age at BMT: 3.6 years (range 0.02-19.5) Mean age at assessment: 15.7 years (range: 6.5-31.8)	Overall performance on all tests within the normal range. But proportion of children (17%) with impaired FSIQ and VIQ (<75) was higher than in the general population	Mothers educational level Hearing deficit (re VIQ) Age at transplant Long absence from kindergarten/primary school	–	Included those treated for extracranial tumours only. Excluded those who had received TBI or CRT
Titman et al. (in press)	N=105 SCID: N=45 ADA: N=13 CID: N=19 WAS: N=10 CHS: N=3 Other immune disorders: N=17	Cross sectional; WPPSI-III; WISC-III; WAIS-III administered 1.1-25 years post BMT (mean 7.7 years) Sibling control group: N=22	Mean age at BMT: 3.6 years Mean age at evaluation: 11 years (range: 3.5-25)	Results for all groups significantly below population norms and sibling controls	Underlying molecular diagnosis; Parental consanguinity; Admission to PICU; SES; English as second language	Age at transplant; Conditioning regimen	Included only those treated with BMT for congenital immunodeficiency. None received TBI or CRT

*Note:* ADA = Adenosine Deaminase Deficiency; ALL = Acute Lymphoblastic Leukaemia; ANLL = Acute Non-Lymphocytic Leukaemia; CHS = Chediak Higashi Syndrome; CID = Combined Immunodeficiency; CML = Chronic Myelogenous Leukaemia; CNS = Central Nervous System; CRT = Cranial Radiation Therapy; F-up = Follow Up; GVHD = Graft Versus Host Disease; MHD = Malignant Haematological Disorder; NMHD = Non Malignant Haematological Disorder; SAA = Severe Aplastic Anaemia; SCID = Severe Combined Immunodeficiency; TBI = Total Body Irradiation; WAIS – R/III = Wechsler Adult Intelligence Scale – Revised/Third Edition; WISC – R/III = Wechsler Intelligence Scale for Children – Revised/Third Edition; WPPSI – R/III = Wechsler Preschool and Primary Scale of Intelligence.

### *Cognitive outcome*

The findings from prospective and multiple case studies, which focussed on assessing change in cognitive functioning over time, are reviewed first, followed by a review of the cross-sectional studies.

Six out of ten prospective and multiple case studies which assessed children pre and one year post BMT (Parth et al., 1989; Phipps et al., 1995; Simms et al., 1998); two years post BMT (Kupst et al 2002) and several years post BMT (Arvidson et al., 1999; Kaleita et al 1989;) found no significant decline in cognitive functioning over time in children treated with BMT. Sample sizes ranged considerably from four (Kaleita et al., 1989) to 153 (Kupst et al., 2002).

In contrast, two studies found that cognitive functioning remained relatively stable at one year post BMT but declined significantly over a longer follow up period. Using a multiple case study design, Smedler et al. (1995) assessed 10 children who were less than three years old at BMT on one to three occasions, at two year intervals post BMT. Results indicated that almost half of these children (N=4) displayed a negative developmental trend over time.

Cool (1996) tested 76 children pre and one year post BMT. A further 45 children were followed up again at four to five years post BMT. A matched control group of children undergoing the major components of cancer treatment (excluding BMT), were assessed at the one year post BMT measurement point and results compared. Results showed average performance on tests pre BMT. At the one year post BMT assessment no significant declines on measures of general intelligence, memory or fine motor skills compared to controls were noted. Follow up at four to five years post BMT however, indicated declining scores over time on all measures, including a three to four fold increase over national levels in the percentage of children identified as having learning difficulties.

A further two studies found the reverse pattern, with cognitive functioning declining significantly at one year post BMT but then showing stability or recovery at three years post BMT. Kramer et al. (1997) assessed 65 children pre and one year post BMT, 26 of whom were later assessed at three years post BMT. Results indicated a significant drop in IQ between baseline and one year follow up, with 43 percent demonstrating a decline in IQ of seven points or more. Relative stability in scores between the one and three year follow up points were noted. However, levels of academic achievement were still significantly below the norms at the three year follow up point. Chou et al. (1996) observed a similar pattern in their results, following assessment of 42 children pre, one and three years post BMT, all of whom had received Total Body Irradiation (TBI) as part of their conditioning regimen.

An additional two studies found that whilst results for the group as a whole showed no significant decline in cognitive functioning following BMT, subgroups within the cohorts were identified as experiencing significant difficulties. This suggests that some patients may be at greater risk for cognitive difficulties following BMT. Kramer et al. (1992) conducted a prospective study of cognitive functioning in children, following low dose cranial radiation for BMT. As a group, no decrements in cognitive functioning one year post BMT were observed. However, examination of individual tests scores indicated that about 25 percent (10/22 participants) experienced a 10 point or greater change in IQ, with the majority (seven) moving in a downward direction and three having decrements of 20 points or more.

Phipps et al. (2000) assessed 102 children pre and one year post BMT, 54 of whom were also assessed at three years' post BMT. No significant changes on global measures of intelligence and academic achievement at either measurement point were observed. However, a significant decline in cognitive functioning was seen over time in children less than three years of age at BMT.

Five studies employed a cross sectional design, assessing paediatric BMT recipients often several years or more post BMT. No evidence of cognitive deficits was found in two of the studies. Halberg et al. (1990) administered a cognitive assessment to six patients treated with BMT at three to 56 months of age, all of whom received TBI. Results indicated normal IQ and appropriate motor co-ordination and language skills development. McGuire et al. (1991) compared 110 patients assessed pre BMT, to 68 patients assessed one-12 years post BMT on standardised measures of IQ and academic achievement. Again all patients had received TBI. No differences between the pre and long term follow up groups were found on any measures.

As with some prospective studies, two cross sectional studies found that whilst overall cognitive functioning in children treated with BMT was within the normal range, there were subgroups experiencing significant difficulties. Smedler et al. (1990) compared 32 BMT recipients one to six years post BMT, to a control group of sibling donors on standardised measures of cognitive functioning. No cognitive deficits were observed in children over 12 years old at BMT. However, compared to controls, impairment on tasks requiring perceptual and fine motor speed was present among the four youngest (<three years) leukaemia patients who had received TBI. This finding, however, is difficult to interpret as an overall developmental assessment was not administered to the youngest children.

Notteghem et al. (2003) assessed 76 children treated with BMT for extracranial tumours between five and 19.3 years following BMT. Children who had received TBI or CRT were excluded from the study. Overall performance on tests of cognitive functioning was within the normal range. However, a proportion of children (17%) had IQ scores that fell within the learning disabled range (<75), significantly higher than the French national average of 2.2 percent.

In the only study to assess cognitive functioning in children treated only for congenital immunodeficiencies, Titman et al. (in press) assessed 105 children, adolescents and young adults 1.1 to 25 years post paediatric BMT. Results of the cognitive tests indicated IQ scores that were significantly below both the population norms and sibling controls. In addition, 25 percent had statements of special educational needs, compared to 2.5 percent in the general population.

#### *Specific areas of neuropsychological functioning*

The studies described focussed on global cognitive outcome, primarily intellectual functioning. However, as mentioned earlier, some also included more focal tests of neuropsychological functioning to identify subtle deficits that might not otherwise show up. Problems following BMT were found on tasks involving perceptual and fine motor speed (Cool, 1996; Parth et al., 1989; Smedler et al., 1990; 1995); memory (Arvidson et al., 1999; Cool, 1996; Parth et al., 1989; Phipps et al., 2000); and executive function (Arvidson et al., 1999; Phipps et al., 2000; Smedler et al., 1995). In addition, difficulties in academic abilities were noted (Cool, 1996; Kramer et al., 1997; Titman et al., in press) with mental arithmetic being identified as being a particular problem for children following BMT (Kupst et al., 2002).

#### *Interim summary*

Given the large variability in results, it is difficult to draw solid conclusions regarding cognitive outcome in children treated with BMT. What does seem apparent, however, is that there are groups of children who do experience significant cognitive difficulties following BMT; there are groups who may not experience global cognitive problems but may show more subtle deficits in particular areas of neuropsychological functioning; finally there are those who seem entirely unaffected by the process. It is therefore important to



identify correlates of cognitive functioning post BMT to gain an understanding of factors that may influence outcome.

#### *Correlates of cognitive functioning in children treated with BMT*

A number of variables, documented throughout the 17 published studies have been found to constitute potential risk and/or resilience factors in the development of BMT related cognitive difficulties. These are grouped into 'illness and treatment related factors' and 'child and family related factors'.

#### *Illness and treatment related factors*

##### *Diagnosis*

Only two studies explicitly examined diagnosis as a correlate of long-term cognitive outcome. Kramer et al. (1992) found no differences between children treated with BMT for SCID (N=9); Neuroblastoma (N=6); Leukaemia (N=6) and Thalassaemia (N=1) at pre and one-year post BMT measurement points. However, the small sample sizes in each diagnostic group challenges the validity of this finding. Using a larger sample of 102 paediatric BMT recipients, Phipps et al. (2000) also reported no relationship between diagnosis and long term outcome at one year post BMT. However, the sample was largely made up of children treated for various types of leukaemia (N=77), with smaller numbers being treated for non-malignancy (N=14) and solid tumours (N=11). Thus, again this result should be interpreted cautiously.

Whilst the sample sizes for individual diagnostic groups were not sufficient to conduct statistical analyses, Kramer et al. (1997) observed a cohort of congenital immunodeficiency patients (N=5) who showed the largest IQ drop (19 IQ points) of any subgroup within their study. Titman et al. (in press) recently conducted a cross sectional study of children treated with BMT for severe congenital immunodeficiencies. As previously mentioned, the average IQ score for the cohort as a whole was significantly below both the population norms and a

sibling control group. This suggests that children treated for congenital immunodeficiency may constitute a diagnostic group at risk of developing long term cognitive difficulties. The large number of patients studied (N=105) also permitted the identification of specific patient groups within the cohort that seemed to be most severely affected. One of the major risk factors identified was the underlying molecular diagnosis. They found that children whose molecular defect was confined to the immune system performed significantly better than those in whom no molecular diagnosis was identified, or in whom the gene defect was more widely expressed. The findings confirmed cognitive deficits in children treated with BMT for Adenosine Deaminase Deficient SCID (ADA SCID), a condition known to be expressed systemically (Rogers et al., 2001). Generalising from this finding, one might hypothesise that in children treated with BMT for other conditions, an important factor affecting outcome may be whether the condition is confined to a particular system or is expressed more widely. Further studies of specific diagnostic groups are needed in order to address this.

#### *Physical late effects*

Whilst the BMT process is associated with a number of physical late effects, few studies have investigated the impact of these on cognitive outcome. Notteghem et al. (2003) explored the effects of hearing loss, a side effect commonly associated with administration of chemotherapeutic agents used in conditioning, and found it to be a major risk factor for defects in verbal IQ. In contrast, Titman et al. (in press), did not find an association between degree of hearing loss and cognitive outcome. However, an incomplete data set regarding this variable may account for the contradictory finding. Additional studies are needed to determine the impact of such physical effects on cognitive outcome.

### *Age at diagnosis/treatment*

Studies of children treated conventionally for leukaemia, indicate that young age at treatment is associated with later cognitive difficulties, suggesting that the younger brain is particularly vulnerable to the neurotoxic effects of conditioning regimens (see Bartlett & Moore, 2005 for a review). Extrapolating from this, age at diagnosis/treatment has been increasingly investigated in the paediatric BMT population. Seven studies reported finding an association between young age (< three years) at diagnosis/BMT and later cognitive difficulties (Arvidson et al., 1999; Cool, 1996; McGuire et al., 1991; Notteghem et al., 2003; Phipps et al., 2000; Smedler et al., 1990, 1995). In addition, some studies have reported specific difficulties with motor functioning in these children (McGuire et al., 1991; Phipps et al., 2000; Smedler et al., 1990, 1995).

Cool (1996) compared children above to children below the age of six at BMT. IQ scores for the younger group were consistently below the population mean of 100, whilst scores for the older group showed a downward trend over time yet remained significantly higher at pre and one year post BMT. The group of children below the age of six at BMT were then split into two groups, those diagnosed before three years of age and those diagnosed after. IQ scores for the older group were at or slightly above the population mean of 100 at each evaluation. In contrast, the scores for the younger group were below the mean and significantly lower than the older group at two years' post BMT.

In contrast, Notteghem et al. (2003) found no differences in global intellectual functioning between children under and above three years of age at BMT. However, a differential effect of age on cognitive outcome was identified. Younger age at BMT was associated with later problems with visual memory and visual spatial deficits, whilst older age at BMT was related to verbal memory deficits.

Six studies did not identify a relationship between age at BMT and later cognitive problems (Chou et al., 1996; Kramer et al., 1992, 1997; Kupst et al., 1999; Simms et al., 1998; Titman et al., in press). However, findings were not clear cut. Both Kramer et al. (1992) and Chou et al. (1996) employed small sample sizes meaning that powerful comparisons between different age groups were not possible.

Using larger sample sizes, Simms et al. (1998) and Kupst et al. (2002) also found that age at BMT did not account for significant amounts of variation in cognitive outcome. However, both studies remarked on the inconsistent pattern of cognitive functioning in serial evaluations for children under three years of age at BMT.

Kramer et al. (1997) and Titman et al. (in press) both found evidence of lower levels of cognitive functioning post BMT, compared to pre BMT levels and normative/sibling control data respectively. Despite having the power to detect group differences, neither study found evidence of a relationship between age at BMT and cognitive outcome. However, critical examination of these studies showed that both samples had a mean age at BMT of 3.5 years. Thus for both studies, the absence of a relationship between cognitive outcome and age at BMT must be viewed in the context of the overall younger age range of these cohorts.

### *Conditioning regimen*

Pre BMT conditioning regimens, generally involving intensive chemotherapy (with or without TBI) to eradicate existing bone marrow and immune function, are neurotoxic. However, the impact of this on the recipient likely depends on factors such as dosage level and period of treatment. Differences in such factors vary according to diagnoses. However, most studies have grouped together children with different diagnoses and hence different conditioning regimens, which will limit the ability to disentangle factors and make causal inferences.

Five studies reported an association between conditioning regimens and cognitive difficulties (Arvidson et al., 1999; Chou et al., 1996; McGuire et al., 1991; Smedler et al., 1990, 1995). Chou et al. (1996) only included children who had been treated with TBI prior to BMT. A significant decline in IQ at one year post BMT was attributed to the toxicities of TBI used in conditioning. However, small numbers at follow up (N=21) and lack of a comparison group limit interpretation of this finding. Studying a cohort of 26 children, Arvidson et al. (1999) reported a significant correlation between intensity of CNS treatment and learning difficulties, as reported by teachers. However, again a small sample size prevents solid conclusions being made.

In contrast, six studies reported no relationship between conditioning regimen and cognitive outcome (Kramer et al., 1992, 1997; Kupst et al., 2002; Phipps et al., 2000; Simms et al., 1998; Titman et al., in press). Kramer et al. (1992) compared 15 children who had received varying doses of CRT with seven who had not received CRT. Results indicated no decrements in cognitive functioning irrespective of whether CRT was used, the dose given or the age at which it was administered. Again, the small sample size is a major limitation. Additionally, the young age of the cohort (mean 2.5 years) precluded assessment of higher areas of cognitive function. Phipps et al. (2000), Kupst et al. (2002) and Titman et al. (in press), all had large enough sample sizes to detect group differences within their cohorts. All failed to find a relationship between conditioning regimens and cognitive outcome.

Cool (1996) also reported that TBI and chemotherapy did not lead to significant declines in cognitive functioning at one year post BMT. However, results indicated that children who had received prior cranial irradiation showed significant declines in IQ post BMT. On the other hand, Phipps et al. (2000) and Kupst et al. (2002) failed to find a relationship between previous CNS therapy and cognitive outcome.

These inconsistent findings contrast with the strong link found between CNS treatment and cognitive difficulties in children treated conventionally for cancer. However, Children treated with BMT generally receive lower doses of radiation than those treated conventionally. Phipps et al. (2000) suggest that there may be a threshold dose of TBI, below which neurotoxicity is clinically insignificant. In addition, as discussed below, there may be interactive effects between factors such as young age and CNS treatment.

#### *Interaction between young age at BMT and CNS treatment*

Young age has been strongly implicated in poor cognitive outcomes following treatment for cancers that involve the CNS (see Bartlett and Moore, 2005 for a review). However, there has been limited data reported on the BMT population regarding the interactive effects of age and CNS treatment. A number of the aforementioned studies that found an effect of young age on cognitive outcome attributed their finding to the young brain being particularly vulnerable to the neurotoxic agents used in the treatment process (Arvidson et al., 1999; McGuire et al., 1991; Smedler et al., 1990, 1995;). However, none of these studies had sample sizes large enough to statistically support this conclusion.

In contrast, five studies found no evidence for an interaction between young age at BMT and treatment variables on cognitive outcome, despite the latter three having enough statistical power to detect such effects (Cool, 1996; Kramer et al., 1997; Notteghem et al., 2003; Phipps et al., 2000; Titman et al., in press). Further well designed studies, using larger sample sizes are needed to determine whether or not certain treatment agents play a significant role in the long-term outcome for very young children treated with BMT.

An alternative explanation for the finding that younger children appear at greater risk for late cognitive effects following BMT is that psychosocial variables, including length of isolation, increased dependency and changes in parenting style may have a negative impact on cognitive development (Kramer et al., 1997). Younger children, who at two or three

years of age are becoming increasingly explorative and entering a critical developmental period, may be particularly affected by such psychosocial and environmental changes. Notteghem et al. (2003) reported that long absences from kindergarten and/or primary school correlated with increases in later cognitive difficulties, which supports this suggestion. It is also consistent with the types of cognitive problems most frequently reported in young children being motor and performance related.

#### *Time since treatment*

Some studies of children treated conventionally for leukaemia suggest that cognitive changes do not emerge until several years post treatment (Mulhern et al., 2001). Consistent with this, McGuire et al. (1991) followed 68 children up to 12 years post BMT and found that more years since first irradiation correlated with decreases in performance IQ. Similarly, Arvidson et al. (1999) assessed 26 children between two and 10 years post-BMT (mean 7 years) and reported that long time since BMT was correlated with low performance on standardised cognitive tests. The length of follow up for most BMT studies may therefore not be sufficient to detect deficits. More studies evaluating cognitive outcome several years post-BMT are needed.

#### *Other treatment related factors*

Other treatment related factors such as type of transplant and presence of and treatment for GVHD have only been investigated in three more recent studies (Kupst et al., 2002; Phipps et al., 2000; Titman et al., In press) all of which found neither factor to be associated with cognitive outcome. Further studies are needed to confirm these findings.

#### *Child and family factors*

Developmental psychopathologists have identified a number of social and demographic variables that seem to constitute general risk and resilience factors across both normative

and clinical samples of children (Cicchetti & Cohen, 1995; Masten & Coatsworth, 1998).

Studies investigating children treated with BMT have included such factors to examine their effects in the context of chronic illness and its treatment.

#### *Pre BMT functioning*

Consistent with findings from the general population that higher IQ serves as a protective factor (Rutter, 1990), pre-BMT levels of cognitive functioning have been shown to be strongly predictive of levels of functioning post BMT (Simms et al., 1998). Similarly, Titman et al (in press), found severity of illness and hence pre-transplant functioning was significantly correlated with cognitive outcome. These results highlight the importance of pre BMT assessments and increased monitoring of children experiencing cognitive difficulties prior to transplant.

#### *Gender*

Several studies have demonstrated an increased vulnerability of females to the cognitive morbidity often associated with conventional CNS treatment for children with cancer (Bleyer et al., 1990; Waber et al., 1990; Von der Weid et al., 2003). In contrast, all studies that investigated gender as a correlate of cognitive outcome following BMT, found it to be non-significant (Chou et al., 1996; McGuire et al., 1991; Phipps et al., 2000; Simms et al., 1998; Titman et al., in press).

#### *Socio-Economic Status (SES)*

Only two studies investigated the effect of SES on cognitive outcome (Kupst et al., 2002; Titman et al., in press). Both found it to be a significant correlate, with children of higher SES doing better in terms of cognitive and academic outcome. Similarly, parental educational level has been identified as an important risk/protective factor for cognitive functioning post BMT (Notteghem et al., 2003). Many areas in developmental



psychopathology highlight that SES has an effect on intellectual and academic functioning (Duncan et al., 1994). Greater parental resources enabling more enriched educational opportunities, such as private tuition, may provide a compensatory effect for some children at risk for cognitive difficulties.

#### *Parental consanguinity*

Titman et al. (In press), identified parental consanguinity as a factor strongly related to lower IQ scores in children treated with BMT for congenital immunodeficiencies. They also found that unaffected siblings from consanguineous pedigrees had significantly lower IQ than unaffected siblings from non-consanguineous families. Thus, this finding is likely due to autosomally inherited traits affecting IQ being carried through in consanguineous pedigrees, rather than being related to the transplant experience itself. High rates of parental consanguinity are often found for children with genetic conditions, such as congenital immunodeficiencies. These children may therefore constitute a subgroup at particular risk for later cognitive problems.

#### *Interim summary*

Findings are not conclusive, mostly due to the methodological constraints of conducting research with a small and chronically ill paediatric population. Across studies the strongest predictor of cognitive outcome appears to be young age at transplant, possibly interacting with the toxicities involved in CNS treatment. In addition, pre-transplant functioning seems important with higher IQ and SES appearing to constitute protective factors. Studies using homogenous samples of children in terms of diagnostic criteria highlight the utility of this approach in allowing for the identification of correlates of outcome specific to a particular diagnostic group (e.g. Titman et al., in press). Further research using homogenous diagnostic samples is needed.

## **Section2: Psychosocial outcome**

Long periods of isolation, diminished contact with peers, disrupted school attendance and cognitive difficulties, together with medical complications sometimes leading to alterations in physical appearance have provided the impetus for research investigating the long term psychosocial functioning of children treated with BMT.

### *Methodological characteristics of psychosocial studies*

Seven studies have investigated various aspects of long term psychosocial functioning following paediatric BMT (see table 2 for an outline of each). For the purposes of this review psychosocial outcome will be explored under the headings: Social Competence; Behavioural/Adaptive Functioning and Emotional functioning. However, in reality these domains are interdependent.

The number of participants studied ranged from 15 (Phipps et al., 1995) to 153 (Kupst et al., 2002) and involved a total of 388 participants. Most involved children presenting with a range of both malignant and non-malignant diagnoses, reducing methodological quality. The exception is Titman et al. (in press) who studied children treated only for congenital immunodeficiencies. Six studies involved children treated with both autologous and allogenic transplants, whilst just one (Arvidson et al., 1999) included only children treated with the former. Five studies specified conditioning regimens (Arvidson et al., 1999; Kupst et al., 2002; Phipps et al., 1995; Phipps & Mulhern, 1995; Titman et al., in press). Of these, the first four studies used samples, consisting of a high percentage of children who had received TBI (mean 80.2%), in addition to chemotherapy. Two studies did not specify conditioning regimens (Barrera et al., 2000; Vanatta et al., 1998), although Vanatta et al. (1998) mentioned that a proportion of children in their sample had received TBI.

Table 2 Chronological Summary of psychosocial outcome in paediatric BMT survivors

Study	sample	Design and measures	Age at BMT; Age at Assessment	Results: Psychosocial outcome	Factors associated with psychosocial outcome	Factors not associated with psychosocial outcome	comments
Phipps, Brenner et al. (1995)	N=64 pre BMT; N=25 6-12 months post BMT ALL: N=4 ANLL: N=9 Other leukaemia: N=6 NHL: N=3 Neuroblastoma: N=1	Prospective longitudinal; CBCL; PHSCS; administered pre and 6- 12 months post BMT. Parent and self report data collected	Mean age: 10.6 years (SD: 5.7; Range: 1.7-23 years)	Sig. decline on measures of social competence post BMT reported by parents. Sig. decline in patient self concept post BMT. Problem behaviour scores showed sig. improvement post BMT.	Visible stigmata associated with BMT		Abbreviated follow up period
Phipps, Mulhern et al. (1995)	N=25 ALL: N=4 ANLL: N=9 Other leukaemia: N=6 NHL: N=3 Neuroblastoma: N=1	Prospective longitudinal; Cross lagged correlational analyses; CBCL; PHSCS; FES administered pre and 6- 12 months post BMT	Mean age: 10.6 years (SD: 5.7; Range: 1.7-23 years)	As above; strong positive correlation between family cohesion and expressiveness and post BMT psychosocial adjustment; family conflict strongly positively correlated with behavioural problems	Family conflict – risk factor  Family cohesion and expressiveness – protective factors		As above
Vanatta et al. (1998)	N=48 (initial cohort of 55) Leukaemia: N=22 Anaemia: N=13 ST: N=8 Lymphoma: N=4 SCID: N=1 control group of classroom peers (N=48)	Case controlled cross- sectional design; social functioning assessed through Revised Class Play; Three Best Friends; and Liking Rating Scale. Peer, teacher and self report data collected.	Mean age at BMT: 8.1 years  Mean age at evaluation: 11.7 years	Compared to controls, BMT survivors described by peers as more 'socially isolated' and 'withdrawn', 'less attractive' and 'less athletically competent'. BMT survivors - fewer best friend nominations and less likely to have reciprocated friendships.	Physical appearance  Athletic ability  Having received WBRT or TBI	Time elapsed since BMT	

Study	sample	Design and measures	Age at BMT; Age at Assessment	Results: Psychosocial outcome	Factors associated with psychosocial outcome	Factors not associated with psychosocial outcome	comments
Arvidson et al. (1999)	N=26  ALL: N=18 AML: N=4 Lymphoma: N=4	Cross sectional; 'I think I am'; CBCL; Rutter Questionnaire administered median 7 years post BMT (range: 2-10 years). Parent, teacher and self report data collected.	Median age: At BMT: 9.8 years At assessment: 16 years (range: 7-24 years)	Compared with normative data: social competence sig. lower; internalising behaviour problems sig. higher	Intensity of CNS treatment	Age at BMT  Length of treatment	Only assessed patients who underwent autologous BMT.
Barrera et al. (2000)	N=26 children and their parents	Prospective longitudinal; CBCL; FACES-III administered pre and 6 months post BMT. BDI and BAI administered to mothers at both time points.	Mean age at BMT: 8.5 years (SD: 5.73; Range: 10 mo-17.5 years)	Behavioural adjustment remained within normal range across time. Mother's psychological adjustment improved over time but was unrelated to children's behavioural adjustment; increased family expressiveness associated with increased behavioural problems	Pre transplant adaptive functioning; Absence of maternal depression; Higher levels of family cohesion and expressiveness	Pre BMT maternal anxiety or depression; Diagnosis; Time since diagnosis; Age at BMT; Type of transplant; Symptom severity	Limited follow up period

Study	sample	Design and measures	Age at BMT; Age at Assessment	Results: Psychosocial outcome	Factors associated with psychosocial outcome	Factors not associated with psychosocial outcome	comments
Kupst et al. (2002)	N=153, 1 year post BMT (initial cohort 377) N=74, 2 years post BMT ALL: N=62 ANLL: N=22 SAA: N=22 CML: N=13 Other: N=30	Prospective longitudinal; CBCL administered pre, one year and two years post BMT	Mean age at BMT: 9.6 years (SD: 5.3 years)	All behaviour means within the normal range with no sig. changes over time	Pre-BMT functioning; Age- social competence; FSIQ – social competence; Previous diagnosis of a learning difficulty – social competence; Higher SES	Age – behavioural functioning; Gender; Diagnosis; Type of treatment	
Titman et al. (in press)	N=105 (initial cohort 117) SCID: N=45 ADA: N=13 CID: N=19 WAS: N=10 CHS: N=3 Other: N=17	Cross sectional; SDQ; Connor's Rating Scale; ABAS administered a mean of 7.7 years post BMT (Range: 1.1-25)	Mean age at BMT: 3.6 years  Mean age at evaluation: 11 years (range: 3.5- 25)	25% children experiencing clinically significant emotional and behavioural problems and lower levels of adaptive functioning. Sig. problems with peer relationships compared to normative data	SES; IQ; Diagnosis of ADA SCID	Gender	Only examined children treated with BMT for immune deficiencies. Thus no TBI administered

**Note:** ABAS = Adaptive Behaviour Assessment Scale; ADA = Adenosine Deaminase Deficiency; ALL = Acute Lymphoblastic Leukaemia; ANLL = Acute Non-Lymphocytic Leukaemia; BAI – Beck Anxiety Inventory; BDI = Beck Depression Inventory; CBCL = Child Behaviour Check List; CHS = Chediak Higashi Syndrome; CID = Combined Immunodeficiency; CML = Chronic Myelogenous Leukaemia; CNS = Central Nervous System; FACES-III = Family Adaptability and Cohesion Evaluation Scale – Third Edition; FES = The Family Environment Scale; FSIQ = Full Scale Intelligence Quotient; NHL = Non Hodgkins Lymphoma; PHSCS = Piers-Harris Self Concept Scale; SAA = Severe Aplastic Anaemia; SCID = Severe Combined Immunodeficiency; SDQ = Strengths and Difficulties Questionnaire; SES = Socio – Economic Status; ST = Solid Tumours; TBI = Total Body Irradiation; WBRT = Whole Body Radiation Therapy.

Mean age at BMT was 8.0 years, ranging from a mean of 3.6 (Titman et al., in press) to 10.6 years (Phipps et al., 1995). Four studies employed a prospective, longitudinal design, following children up at six months (Barrera et al., 2000); one year (Phipps et al., 1995; Phipps & Mulhern, 1995) and two years post BMT (Kupst et al., 2002). Three studies used cross sectional designs (Arvidson et al., 1999; Titman et al., in press; Vanatta et al., 1998), with mean time between BMT and assessment being 6.5 years, ranging from 3.6 years (Vanatta et al., 1998) to 7.7 years (Titman et al., in press). Two of these used control groups of classroom peers (Vanatta et al., 1998) and siblings (Titman et al., in press).

Eligibility criteria differed between the studies. Two required children to be in complete remission for one year (Titman et al., in press) and two years (Arvidson et al., 1999), whilst one specified that participants must have returned to school full time (Vanatta et al., 1998). Regarding exclusion criteria, two studies excluded children treated with BMT for brain tumour (Phipps et al., 1995; 1995) due to considerable differences in illness and treatment related factors in this group of children. Three studies excluded children treated for Severe Combined Immune Deficiencies (Barrera et al., 2000; Phipps et al., 1995; Phipps & Mulhern, 1995) due to marked differences in the period of isolation compared to that for other diagnoses. One study excluded children receiving full time special education services, due to small classroom sizes compromising the validity of the study design (Vanatta et al., 1998).

As with the studies investigating cognitive outcome, considerable variability between study methodologies, limits the ability to directly compare and contrast findings and hence identify reliable correlates of outcome.

Regarding assessment, six studies included measures of social competence (Arvidson et al., 1999; Kupst et al., 2002; Phipps et al., 1995; 1995; Titman et al., in press; Vanatta et al., 1998). Six studies used measures of behavioural/adaptive functioning (Arvidson et al., 1999;

Barrera et al., 2000; Kupst et al., 2000; Phipps et al., 1995; Phipps & Mulhern, 1995; Titman et al., in press). Three studies included an assessment of self esteem (Arvidson et al., 1999; Phipps et al., 1995; Phipps & Mulhern, 1995). All measures were standardised, allowing more reliable and valid conclusions to be drawn. Increasingly, recent studies have moved away from using self report and/or a single informant, usually the mother, to gathering information from multiple informants, including teachers (Arvidson et al., 1999; Titman et al., in press; Vanatta et al., 1998) and peers (Vanatta et al., 1998). This inclusion of data from more objective and school based sources seems important given the disruption to schooling and peer contact that BMT results in.

#### *Psychosocial outcome*

##### *Social functioning*

Five of six studies assessing social competence found evidence of lower levels of functioning following BMT (Arvidson et al., 1999; Phipps et al., 1995; Phipps & Mulhern, 1995; Titman et al., in press; Vanatta et al., 1998). Phipps et al. (1995) assessed 15 BMT survivors pre and six to 12 months post BMT. A near significant trend towards declining social competence from pre to post-BMT was identified. Post transplant scores indicated a mild to moderate degree of dysfunction, with mean scores comparable to those of a clinically referred population. The small sample size (N=15) however, limits the validity of this finding.

Using a much larger sample, assessing BMT survivors several years post-BMT and using multiple informants (parent, teacher, child) Titman et al. (in press), found scores for the peer relationships domain of the SDQ (Goodman, 1997) to be significantly higher than normative data for both boys and girls when rated by parents and for just girls when rated by teachers. These results preliminarily suggest that peer relationships may be a particular area of social competence affected post BMT, in children treated for congenital

immunodeficiencies. However, the SDQ is a brief assessment tool and the peer relationships domain consists of only 5 questions. This challenges the reliability of the conclusions made.

Despite the centrality of peer relationships to normal social and emotional development and the strong record of reliability and predictive validity of peer nominations (Parker & Asher, 1987), only one study used classroom peers as informants. Using the Revised Class Play (RCP, Masten et al., 1985); Three Best Friends (Bukowski & Hoza, 1989); and the Liking Rating Scale (Asher et al., 1979), Vanatta et al. (1998) compared 48 paediatric BMT recipients to 48 non-chronically ill, same classroom, same gender comparison peers. Relative to comparison controls, BMT recipients were described by peers but not teachers or themselves, as more socially isolated and withdrawn. In addition, peers described them as 'sick alot', 'missing school', 'less attractive' and 'less athletically competent' than comparison peers. Sociometric ratings indicated that whilst BMT survivors were not disliked overall, they received fewer best friend nominations and were less likely to have reciprocated friendships. Both Vanatta et al. (1998) and Titman et al. (in press) employed cross sectional designs, which do not permit monitoring of change over time. This makes it difficult to ascertain whether their findings are due to the BMT process or to other factor(s).

In contrast to the above findings, Kupst et al. (2002) assessed 153 children one year post BMT, 74 of whom were followed up at two years post BMT. Results indicated social competence, as rated by parents, to be within the normal range with no significant changes over time. The only measure used to assess social competence, however, was the Child Behaviour Check List (CBCL; Achenbach, 1991). Whilst this is a widely used, standardised measure, it only allows for data to be collected from a single informant (the parent), which limits the validity of the finding.



### *Behavioural/adaptive functioning*

Five studies used the CBCL to assess behavioural functioning (Arvidson et al., 1999; Barrera et al., 2000; Kupst et al., 2002; Phipps et al., 1995; Phipps & Mulhern, 1995). Findings across studies were mixed. Two studies reported behavioural scores within the normal range pre and six months (Barrera et al., 2000), one and two years post BMT (Kupst et al., 2002) with no significant changes over time.

Phipps et al. (1995) found that behavioural scores were within the normal range pre BMT and showed significant improvement after transplant. This improvement in behavioural functioning was found in conjunction with the significant decline in social functioning described earlier. Phipps et al. (1995) explained these findings as possibly resulting from enforced social isolation and physiological debilitation during BMT and for some time afterwards. These social and physical restrictions may lead to a diminution of all behaviour, resulting in decreased opportunity for both social interaction and problem behaviours. Thus improvement in scores would be seen on measures consisting of entirely negative behaviours. The fact that children were followed-up at only six to 12 months post-BMT lends support to this hypothesis.

In contrast, Arvidson et al. (1999) reported increased behavioural problems among school aged children post BMT compared to normative data, as rated by parents. In particular, higher scores for internalising than for externalising behaviour problems were reported. Teachers also reported an increase in behaviour problems, the most commonly endorsed item on the Rutter Questionnaire (Rutter, 1967) being 'has poor concentration or short attention span'. Whilst this finding has been reported by Arvidson et al. (1999) as 'behavioural problems', given the higher scores for internalising problems, it may be that

parents and teachers are identifying emotional distress and attention difficulties, rather than 'acting out' behavioural problems.

Using the conduct and hyperactivity domains of the SDQ, Titman et al. (in press), reported 25 percent of their cohort as scoring above threshold, indicating clinically significant behavioural difficulties, compared to 10 percent in the general population. Significantly higher levels of concentration, attention and hyperactivity problems than normative data, were reported by both parents and teachers. Significantly lower levels of functional skills were found in the BMT children compared to normative data.

To summarise, the findings regarding behavioural outcome are inconsistent. It seems that up to two years post BMT, behavioural functioning remains stable or even improves.

However, results from studies assessing children several years post-BMT suggest an increase in behavioural problems compared to normative data. Again, the latter two studies employed cross sectional designs which do not permit causal inferences to be made.

Nevertheless, it is an important finding and is consistent with the suggestion from some studies, investigating long-term cognitive outcome, that difficulties may take several years to emerge. Indeed, cognitive and behavioural outcome following BMT are likely to be closely linked, as evidenced, for example by the strong correlation between IQ and SDQ scores found by Titman et al. (in press).

### *Emotional functioning*

Regarding self esteem following BMT, Phipps et al. (1995) reported a decline in patient adjustment and overall self concept. In comparison to normative data, the BMT children showed a very positive self concept before transplant, which declined but remained within normal limits after transplant. However, the magnitude of the decline was highly significant, despite the small sample size of 15. Children treated with BMT perceived

themselves as being more anxious, less competent in school and intellectual activities, less popular with peers and more unhappy after BMT.

Arvidson et al. (1999) also found that self-reported levels of self esteem among BMT children were equal to those reported in a normative sample. However, the cross sectional design employed did not allow for change over time to be measured and thus it is not known whether these children also experienced a decline in self esteem compared to pre BMT levels.

A number of studies using self report measures to assess paediatric cancer patients suggest that findings of normal levels of self esteem should not be taken at face value (e.g. Canning et al., 1992). Such studies have described lower levels of self reported depression and anxiety in paediatric cancer patients than healthy children, and suggest that this population manifests an exaggerated use of denial and need to present themselves in a good light when completing such measures. Thus, the significant decline in self reported self esteem following BMT, described by Phipps et al. (1995), appears the most clinically relevant finding and one which is consistent with parent-reported declines in social competence in this sample of children.

#### *Interim summary*

The main conclusions that can be drawn thus far are that a significant number of paediatric BMT survivors seem to experience psychosocial difficulties following transplant. Social functioning appears to be most implicated, with difficulties present in some samples up to several years post BMT. As noted earlier, behavioural functioning post transplant appears to remain stable or improve immediately post transplant, but may then decline with longer time since transplant. This hypothesis, however, is based on findings from a limited number of studies and further research is needed to confirm this pattern. Findings regarding self esteem suggest that it is within the normal range but that this should be interpreted

cautiously given the reported use of avoidance and denial and need these children may have to present themselves as functioning well, as suggested in the cancer literature. Alternatively, having survived a life threatening illness may result in adjustment of judgements and expectations.

#### *Correlates of psychosocial functioning following BMT*

A number of the studies reviewed identified variables found to be related to long-term psychosocial outcome in children treated with BMT. These are described below, again grouped under the headings of 'illness and treatment related factors' and 'Child and family related factors'.

#### *Illness and treatment related factors*

##### *Diagnosis*

Two studies examining the psychosocial outcome for children treated with BMT found no significant relationship between diagnosis and outcome at 6 months (Barrera et al., 2000) and 2 years post BMT (Kupst et al., 2002). In both studies, however, the majority of children were treated for leukaemia with much smaller groups of children being treated for other forms of haematological malignancy. Thus, differences between diagnostic groups cannot be ruled out.

Examining outcome for children treated for congenital immunodeficiency, Titman et al. (in press), found that children treated for ADA deficient SCID had significantly worse scores on measures of behavioural, social and emotional functioning than those treated for other forms of congenital immunodeficiency. As mentioned previously, ADA SCID is systemically expressed, rather than being confined to the immune system and is associated with a number of non-immunological deficits, which have been well documented (Rogers et al., 2001). This illustrates the link between cognitive and behavioural functioning found in this

group of children. In addition, it emphasises, the utility of employing homogenous diagnostic samples in identifying at risk subgroups of children.

#### *CNS treatment*

Kupst et al. (2002) found no association between type of treatment and psychosocial outcome in their sample of 153 children assessed at one year post and 74 children at two years post-BMT. Most of the sample (93%) underwent TBI, however, making it difficult to have a powerful comparison with those who did not receive TBI. Given the absence of psychosocial difficulties noted in this particular sample, this finding seems to suggest that the typical doses of TBI used in BMT may not result in the psychosocial difficulties sometimes seen following conventional treatment (see Patenaude & Kupst, 2005 for a review)

In contrast, two cross-sectional studies found a significant relationship between intensity of CNS treatment/use of TBI and psychosocial difficulties (Arvidson et al., 1999; Vanatta et al., 1998). Arvidson et al. (1999) found that low social competence and internalising behavioural problems, as reported by parents, correlated to CNS treatment intensity. It should be noted that nine of the 19 patients who were treated with TBI (total N= 26) had received prior cranial irradiation, suggesting a longer history of illness and intensive treatment than described for the sample studied by Kupst et al. (2002). Vanatta et al. (1998) found that differences between the BMT and comparison groups on peer reports of passive/anxious behaviour varied as a function of whether or not Whole Body Radiation Therapy (WBRT)/TBI had been administered. In particular, BMT survivors who had received cranial radiation were perceived as more passive, anxious and socially withdrawn than those who had not received cranial radiation. This is consistent with literature suggesting that children treated with cranial radiation for brain tumours are at risk for social withdrawal (Noll et al., 1992). Further work is needed to examine the role of specific

deficits in social information processing or problem solving that may explain the apparent impact of cranial radiation on social isolation and withdrawal.

Other illness and treatment related factors that have been investigated and found not to be associated with psychosocial outcome are symptom severity; type of transplant (both Barrera et al., 2000) and the length of the treatment period (Arvidson et al., 1999).

#### *Age at BMT*

Two studies found that age at BMT was not significantly associated with behavioural and social functioning (Arvidson et al., 1999; Barrera et al., 2000). However, Kupst et al. (2002) found that, whilst age at BMT was not significantly associated with behavioural functioning, it was associated with social competence, with older children having higher social competence scores at one year, but not at two years' post BMT. The authors suggest that older children may return to school and social activities more quickly than do younger children.

#### *Time since BMT*

Three cross sectional studies found that time elapsed since BMT was not significantly associated with psychosocial functioning (Arvidson et al., 1999; Titman et press; Vanatta et al., 1998). All studies assessed participants several years post BMT and reported higher levels of behavioural and social difficulties in BMT survivors than comparison peers and normative data. Thus, these findings suggest that some children may experience unremitting difficulties and not just short-term struggles with school re-entry after a lengthy absence. Vanatta et al. (1998) suggest that BMT, in addition to prior treatment experiences, might initiate unfolding dysfunctional transactions between the child and the environment that disrupts social development. Thus, initial reasons for diminished peer contact, such as hospitalisation may alter social self perceptions, attributions and

expectancies in a way that would negatively affect social initiation and behaviour. If initial social difficulties were to continue unchecked, children would likely fail to learn and practice skills central to making and keeping friends.

#### *Child and family related factors*

##### *Physical appearance*

Two studies have reported that children whose physical appearance is altered as a result of the BMT process are at higher risk for problems with peer acceptance and social integration (Phipps et al., 1995; Vanatta et al., 1998). Vanatta et al. (1998) found that changes in appearance and athletic ability mediated the impact of BMT on peer perceptions of active isolation and social acceptance. Vanatta et al. (1998) also highlight the differences between the information provided by peers and teachers with respect to these variables. In particular, they reported that the data provided by teachers suggest that they underestimate peer relationship difficulties for these children and consequently may be unlikely to initiate a request for intervention.

##### *Pre-BMT psychosocial functioning*

Two prospective studies reported a significant association between pre-BMT levels of psychosocial functioning and levels of psychosocial functioning at six months (Barrera et al., 2000) and one and two years post BMT (Kupst et al., 2002). Thus, from a resilience standpoint, higher levels of social and behavioural functioning, prior to BMT, seems to strengthen functioning in these areas post BMT. Clinically, this underscores the need for pre BMT assessments of functioning, followed by close monitoring post BMT of those identified as functioning at lower levels pre BMT.

### *IQ, SES, & Gender*

Lower IQ was a strong predictor of poorer outcome with regard to psychosocial functioning (Kupst et al., 2002; Titman et al., in press). In addition, Kupst et al. (2002) found that children with a previous diagnosis of a learning disability were significantly lower in social competence.

Two studies investigated the effect of SES on psychosocial functioning (Kupst et al., 2002; Titman et al., in press). As would be expected from findings reported in the general child literature (Rutter, 1990), both found that children of a higher SES tended to fare better in terms of psychosocial functioning post-BMT.

Two studies examined gender as a correlate of psychosocial functioning (Kupst et al., 2002; Titman et al., in press). Both found no relationship between gender and psychosocial functioning.

### *Family functioning*

Employing cross-lagged correlational analyses within a prospective longitudinal design, Phipps & Mulhern. (1995) used the Family Environment Scale (FES, Moos, 1981) to investigate the effect of perceived family environment as a determinant of psychosocial adjustment in children undergoing BMT. Prior to BMT, perceptions of family conflict showed a moderate inverse correlation with scores on measures of psychosocial functioning, whereas family cohesion and expressiveness were unrelated or weakly related with these measures. In contrast, all pre BMT family environment variables were highly predictive of psychosocial functioning post-BMT. Family expressiveness and cohesion appeared to act as protective factors, exerting a greater influence during a high stress period than before the onset of the stressor, whereas family conflict acted more directly as a risk factor whose negative impact was expressed regardless of stress level. In addition,



the variable of Expressiveness was the only subscale to show a significant change post-BMT. The authors suggest that this finding indicates that managing the stresses of BMT demands a high level of expressiveness, conferring an advantage to those families whose pre-morbid expressiveness was high and impelling increased expressiveness in others as a result of negotiating the demands of BMT.

Barrera et al. (2000) also investigated the effects of family functioning on psychosocial functioning following BMT. Family functioning was measured using the Family Adaptability and Cohesion Evaluation Scale (FACES-III, Olson et al., 1985). With regard to the relationship between family cohesion and behavioural functioning, results were in contrast to those of Phipps and Mulhern (1995) in that higher levels of pre-BMT family cohesion were associated with reports of more behavioural problems at pre and six months post-BMT. However, both the family cohesion and child behavioural mean scores were within the normal range at both pre and post-BMT. Given that scores were within the normal range, the authors explained the contradictory finding as suggesting that increased family cohesion pre-BMT may have facilitated healthy/normal 'acting out' in this group of children that was still evident six months post BMT.

#### *Maternal psychological functioning*

Research has demonstrated a strong relationship between parental mental health and child adjustment to chronic illness (Dockerty et al., 2000; Sahler et al., 2002). This has contributed to an increased focus on parental response to BMT. Thus far, findings suggest that there are subgroups of parents at higher risk for increased distress during the acute phase of transplant (Phipps et al., 2005). Significant predictors of parental distress include prior parent and patient illness-related distress, pre-morbid child internalising behavioural problems, and parental avoidant coping behaviours (Phipps et al., 2005). Of the studies reviewed, only one examined the relationship between maternal mental health and the

child's behavioural adjustment post-BMT (Barrera et al., 2000). Contrary to findings from previous studies that have investigated psychological symptomatology in parents of children with cancer (Barakat et al., 1997; Kazak et al., 1997), results showed no relationship between pre or post BMT maternal anxiety or depression and long term psychosocial adjustment in paediatric BMT survivors. However, low levels of depressive symptoms and only mildly elevated levels of anxiety at time of transplant that returned to normal by six months post-BMT, were reported in this sample of mothers. The finding of no relationship between maternal mental health and child adjustment must therefore be interpreted with this in mind.

#### *Interim summary*

As with cognitive outcome, limited conclusions can be drawn regarding correlates of psychosocial outcome. Despite fairly consistent findings of difficulties with social functioning post BMT, particularly regarding peer relationships, the mechanisms underlying this are as yet unclear. It may indicate specific difficulties in socialisation as a consequence of prolonged hospitalisation and isolation during treatment at a young age. However, other variables such as appearance and cognitive ability (influenced by CNS treatment) have also been suggested as possible correlates. As with cognitive outcome, higher levels of pre BMT psychosocial functioning, and higher IQ and SES appear to constitute protective factors. Family functioning appears important in influencing psychosocial functioning post transplant, with conflict being identified as a risk factor and cohesion and expressiveness serving as protective factors.

#### **Populations at risk**

The current state of research suggests further work is needed before it will be possible to reliably identify specific groups of children at risk for later cognitive and/or psychosocial difficulties. However, a few hypotheses can be made based on what is already known.

Firstly, whilst separated in this review, it is clear that cognitive and psychosocial outcomes are linked. Children who are experiencing cognitive difficulties, evidenced by lower IQ and/or learning disabilities, perhaps related to undergoing transplant at a young age in conjunction with intensive CNS treatment (involving cranial radiation) also appear to experience psychosocial difficulties. Children from families demonstrating high conflict, where expressiveness and cohesion are low, and particularly those of lower SES may also be at greater risk for cognitive and psychosocial difficulties post transplant. Finally, it appears that pre-transplant measures of cognitive and psychosocial functioning are strong predictors of post transplant functioning. This underscores the need for pre transplant assessments of these domains of functioning in order to identify those who may be at greatest risk for later difficulties. Given the relationship between family functioning and child adjustment, it would be useful to include measures of family functioning in these pre and post BMT assessments.

### **Methodological critique**

As already mentioned, the difficulty in drawing reliable conclusions from the current evidence base is partly due to the many logistical difficulties in carrying out systematic research with this paediatric population. It is therefore useful to explore a number of methodological issues which may account for some of the inconsistencies and variations observed.

#### *Study design*

A number of studies employed prospective designs with repeated measures which allow for comparisons between pre and post BMT assessments and help to determine whether functioning improves or declines over time. However, since BMT is still a relatively new medical procedure and until recently mortality rates were high, a number of early prospective studies were limited by large rates of attrition due to death. Sample sizes at the

post BMT measurement points were often small, reducing the validity of findings. It was also not always clear which participants were evaluated at which points in time.

Other studies used cross sectional design which afford numerous benefits including larger sample sizes due to reduced attrition rates, plus they are relatively inexpensive and time effective. However, the major disadvantage is that it is not possible to ascertain directions of causality when explored within a single time point, as important effects may emerge over time due to several possible causal influences and/or interactions between a multitude of risk and resilience factors.

### *Sampling issues*

The extent of heterogeneity in the BMT samples was striking. Due to the limited number of long term paediatric BMT survivors, sample sizes varied considerably with many being small. Significant findings derived from smaller samples may be more vulnerable to type 1 error, thus compromising their reliability. Alternatively, significant findings may be missed due to insufficient statistical power to detect small effect sizes. Small sample sizes are also particularly problematic when examining predictors of outcome, since statistical power is further reduced when samples are broken down into subgroups based on medical or demographic variables.

Most studies used samples comprising children with a wide variety of diagnoses, thus often overlooking respective differences in illness chronicity, pre-BMT treatment therapies, number of relapses, length of hospitalisation and functional outcome. There was also extensive variability in time since diagnosis and/or treatment both within and between studies. In addition, the wide age ranges within and between studies necessitated the use of different assessment instruments at different developmental levels. This is particularly an issue for prospective longitudinal studies whereby a child may have been evaluated

using one instrument pre BMT and scores compared to performance using a different instrument post BMT.

#### *Comparison groups:*

Failure to include appropriate comparison groups is a prevailing weakness in BMT outcomes research (Tsimicalis et al., 2005). A few studies used sibling/donor control groups, however, only one study (Cool, 1996) included a control group who also underwent a similar therapy and faced a life threatening disease.

### **Directions for future research**

What is clear from the current literature on cognitive and psychosocial outcome following paediatric BMT is that findings are fairly inconsistent. This prevents the establishment of a coherent body of knowledge from which to inform and guide clinical assessments and interventions. Although it is evident that a significant number of children experience long term and sometimes unremitting difficulties following BMT, the exact nature of these difficulties and the specific mechanisms underpinning them need to be more clearly identified.

Future research needs to focus on discrete BMT populations. Only two of the studies used homogenous diagnostic populations (Notteghem et al., 2003; Titman et al., in press). In order to obtain large enough data bases from which to draw reliable conclusions, future research may need to initiate multicentre studies. This would pose its own set of challenges, such as ensuring good comparability in methodological procedures. In addition, to date the majority of studies have focussed on global areas of functioning. More work is needed to investigate the subtle difficulties within specific domains of functioning that the current literature suggests may be present. This is particularly the case for cognitive

outcome, where the majority of studies have focussed on intelligence and academic data and have not sought to empirically examine higher order areas of neuropsychological functioning.

More prospective longitudinal studies with larger sample sizes and longer follow up periods are warranted to effectively delineate and disentangle specific causal pathways and assess change over time in this population. Whilst a number of studies were able to identify correlates of outcome, only two studies sought to identify predictors of adjustment using a cross lagged correlational approach (Barrera et al., 2000; Phipps & Mulhern., 1995). This approach allows one to assess whether the effect of a variable on, for example, adjustment before the onset of a stressor (e.g. BMT) differs from the effect during the high stress period. Most real life stressors do not lend themselves to such an approach, because they can either not be anticipated, or they lack a relatively discreet onset. A few rare situations such as a planned medical procedure, like BMT, provide an opportunity to use such a longitudinal approach to identify risk and resilience factors.

Regarding implications for clinical practice the incorporation of cognitive and psychosocial assessments into routine clinical practice appears essential in order to identify patient subgroups that may need additional support and intervention. Pre-BMT assessments, where possible, seem particularly important

Finally, it is important to work towards developing a theoretical or conceptual framework for understanding and anticipating individual differences in psychological and behavioural responses to BMT. Once this stage has been reached, research should then move towards applying some of the knowledge gained by empirically investigating intervention strategies for this patient population. This is already being done with some success in conventional paediatric cancer research (Butler & Mulhern., 2005; Kazak, 2005).

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## **‘Part 2: Empirical Paper’**

### **‘Social Competence and Executive Function in Children treated with Bone Marrow Transplant (BMT) for Congenital Immunodeficiency’**

## **Abstract**

**Objective:** The purpose of this study was two-fold: to investigate further the difficulties in social competence that have previously been reported in children treated with bone marrow transplant (BMT); and, to explore two main potential underlying mechanisms, suggested in the literature: (1)cognitive processes in the form of executive dysfunction; and (2) non-social attributes of physical appearance and athletic ability.

**Method:** Thirty-one children (8-16 years of age), treated with BMT for congenital immunodeficiency were assessed on measures of social competence, executive function, and physical appearance/athletic ability. Results were compared to a control group of thirty-one non-chronically ill children, matched for age, gender, ethnicity and IQ. Parent, teacher and self report data were collected.

**Results:** Relative to controls, BMT survivors were described by parents and teachers, but not by themselves' as experiencing difficulties with social functioning. Performance on tests sensitive to executive dysfunction was not significantly correlated with measures of social competence. However, an objective measure of physical appearance, rated by clinicians was significantly correlated with all teacher-report measures of social competence.

**Conclusions:** Results suggest that children treated with BMT for congenital immunodeficiency are experiencing significant difficulties in social functioning, not solely accounted for by below average intelligence. Regarding the mechanisms underpinning these problems, most evidence currently points towards the non-social attributes of altered physical appearance and athletic ability. This has clear clinical implications with regard to identifying those children who may be at increased risk for later difficulties with social competence, and developing appropriate interventions.



## Introduction

### *Congenital Immunodeficiencies*

Severe Combined Immunodeficiencies (SCID) are an extremely rare, heterogenous group of inherited conditions in which defects in the immune system result in an inability to fight infection. In addition, there are other non-SCID immunodeficiencies, such as Wiskott Aldrich Syndrome and Hyper IgM syndrome that also have profound immune defects and together the group is termed severe congenital immunodeficiencies (Fischer et al., 1997). Children with a congenital immunodeficiency experience multiple infections, resulting in a failure to grow and gain weight as expected (i.e. failure to thrive). Left untreated, they rarely live past the age of two years.

Until recently reconstitution of the immune system by bone marrow transplantation (BMT) has been the recommended and only curative option for congenital Immunodeficiencies. At present this remains the most common form of treatment, although a small but increasing number of children are now being treated with gene therapy. The European Society for Immunodeficiency (ESID) database established in 1968, shows that to date over 1000 patients have undergone BMT, although this may be a significant underestimate due to reporting failure (ESID – Working Party on Inborn Errors – Communication). Only two centres in the UK, Great Ormond Street Hospital and Newcastle General Hospital provide services for children suffering from a congenital immunodeficiency. Approximately 30 children with severe congenital immunodeficiency are treated with BMT at Great Ormond Street Hospital each year.

### *Bone Marrow Transplant (BMT)*

The bone marrow transplant procedure for congenital immunodeficiency involves the use of chemotherapy to eradicate existing bone marrow and immune function. Following this,

the patient is given an infusion of healthy marrow stem cells. For a minimum of two to four weeks, patients have no functioning bone marrow. During this time frame, numerous toxic side effects are common, including nausea, pain, infections and even major organ failure. Hospitalisation typically lasts one to two months, during which time the child is in 'isolation', and contact with others is severely limited. After discharge, contact with non-family members is restricted due to protracted poor immune system functioning. The majority of children with a congenital immunodeficiency are treated with BMT before the age of three years, however, for older children school attendance is often not allowed for three to nine months following discharge and can result in an entire academic year being missed.

BMT is a difficult ordeal with the acute phase being characterised by considerable psychological distress for both child and family (see Powers et al., 1996 for a review). As increased numbers of children have become long term survivors of BMT, research has now begun to focus on their psychological adjustment post transplant.

#### *Social functioning of paediatric BMT survivors*

Peer relationships are the primary context in which children learn co-operation, negotiation and conflict resolution skills that are essential for normal emotional and psychological development (Rubkin et al., 1998). Childhood peer problems have been found to predict a wide variety of later negative outcomes including delinquency, dropping out of school, substance abuse, academic difficulties, and psychological maladjustment (Deater-Deckard, 2001; Parker & Asher, 1987; Rubkin et al., 1998). Evidence indicates that the quality of peer relationships is more predictive of later psychological functioning than other variables typically used in mental health research, such as IQ, academic achievements and absenteeism (Hoza, 2007).

Given the prolonged period of isolation during treatment and the restrictions placed on peer contact necessitated by the BMT procedure, the social functioning of paediatric BMT survivors has been increasingly examined (Arvidson et al., 1999; Kupst et al., 2002; Phipps et al., 1995, 2000; Phipps & Mulhern., 1995; Titman et al., in press; Vanatta et al 1998). With few exceptions (Kupst et al., 2002) results suggest that children treated with BMT are at risk for experiencing social difficulties, comparable to those of clinically referred populations. Compared to classmate controls, children treated with BMT have been described by their peers as more socially isolated and withdrawn, and as 'sick alot', 'missing school', and less physically attractive and athletically competent (Vantatta et al., 1998). It has also been reported that compared to pre transplant levels of functioning, children treated with BMT show a decline in adjustment and overall self concept, perceiving themselves as 'more anxious', 'less competent in school and intellectual activities', 'less popular with peers' and 'more unhappy' after transplant (Phipps et al., 1995).

Compared to normative data, children treated with BMT have been described as experiencing significantly high levels of internalising behavioural problems including more fearful, inhibited and over-controlled behaviours (Arvidson et al., 1999). These difficulties are likely to negatively affect these children's ability to initiate peer relationships following extended absences from school and peer related activities. Indeed, Titman et al. (in press), studied children treated with BMT for congenital immunodeficiency and found that scores for peer relationship difficulties were significantly higher than normative data for both boys and girls when rated by parents and for just girls when rated by teachers. In addition, some cross sectional studies conducted several years post transplant have found no relationship between time elapsed since transplant and social functioning (Titman et al., in press; Vanatta et al., 1998). This is concerning as it suggests a pattern of unremitting difficulties and not just short term adjustment problems regarding re-integration into school following an extended absence.

Thus far, despite the evidence that children treated with BMT appear to experience problems with social functioning, methodological problems have made it difficult to identify mechanisms that might be underlying these difficulties. The main problem concerns the considerable heterogeneity of study samples. Children undergoing BMT for different diagnoses, including leukaemia, brain tumour, anaemia and immunodeficiency, which require different pre and post transplant treatment regimes, are often grouped together in order to obtain large enough sample sizes for meaningful statistical analyses. This makes it difficult to reliably identify valid correlates of social functioning in these children. However, examining the evidence base as it currently stands, two main hypotheses can be suggested: first that cognitive difficulties may underlie the social problems experienced by children treated with BMT; Second, that the social difficulties may be mediated by changes in non social attributes of physical appearance and athletic ability.

#### *1. Cognitive ability as an underlying mechanism of social functioning*

Based on a number of studies which have examined the social functioning of children treated for various chronic illnesses, it has been suggested that the children who experience later social difficulties, may be those whose condition or treatment causes damage to their Central Nervous System (CNS) and cognitive abilities (Noll et al., 1999). Whilst the domains of cognitive and psychosocial functioning are often studied separately it is well known that they are not mutually exclusive and instead operate inter-dependently (Patenaude & Kupst, 2005).

Given the aggressive nature of the BMT procedure and the neurotoxic agents used in treatment regimes, the impact of BMT on cognitive outcome has been addressed by a number of studies (Arvidson et al., 1999; Cool, 1996; Chou et al., 1996; Kramer et al., 1992, 1997; Kupst et al., 2002; Notteghem et al., 2003; Phipps et al., 1995, 2000; Simms et al., 1998; Titman et al., in press). The findings in these studies are not consistent and vary from

minimal evidence for cognitive decline in some studies (e.g. Kramer et al., 1992; Kupst et al., 2002) to a significant decrease post transplant in others (e.g. Cool, 1996; Titman et al., in press).

A number of studies have reported a relationship between cognitive and social functioning in paediatric BMT survivors. Vanatta et al. (1998) found that children who received neurotoxic radiation therapy were described by peers and teachers as more passive, anxious and socially withdrawn than children who had not received radiation as part of their treatment. In addition, social competence and internalising behavioural problems in BMT survivors have been found to be significantly correlated to Central Nervous System (CNS) treatment intensity (Arvidson et al., 1999). Furthermore, in children treated for congenital immunodeficiency, a significant association between intellectual ability and social functioning, as rated by parents and teachers was found (Titman et al, in press).

The exact nature of the relationship between cognitive and social functioning in paediatric BMT survivors is currently not clear. First, studies have mostly used intelligence data as a measure of cognitive ability and have not sought to separately examine higher order areas of neuropsychological functioning. It has been proposed, however, that the executive functions of attention, concentration and working memory may be implicated (Phipps et al., 2000). Problems with executive function have been reported to be the most frequently observed cognitive impairment in adult BMT survivors (Booth-Jones et al., 2005; Harder et al., 2002; Meyers et al., 1994). However this has not yet been empirically investigated in paediatric BMT populations. Consequently, it is not known which particular cognitive processes might underpin difficulties with social functioning in this cohort of children.

The construct of executive functioning subsumes those processes that serve to monitor and control thought and action, including self-regulation, planning, cognitive flexibility, response inhibition and resistance to interference (Carlson and Moses, 2001). Critical

developments in children's executive capacities appear to occur during the first year of life, followed by another growth spurt in executive development from about three to seven years of age (Diamond et al., 2002; Gotgay et al., 2002). Notably, the vast majority of children with congenital immunodeficiency undergo BMT before the age of seven, with most being transplanted at less than three years of age.

In addition, many of the cognitive skills that fall under the umbrella of executive function appear to have equivalents at the social competence level. Several studies have demonstrated commensurate deficiencies in executive function and difficulties in domains of social functioning, for example distractibility, impulsivity, lack of concentration and problems recognising the consequences of actions (Hughes, 2002; Morgan & Lilienfeld, 2000). A concurrent negative association has also been reported between executive abilities and social competence dysfunction, in childhood disorders, such as attention deficit hyperactivity disorder (Fisher et al., 2005), conduct disorder (Seguin et al., 1999) and autism (Lopez et al., 2005).

## *2. Physical appearance and athletic ability as mediators of social functioning*

Physical appearance has long been identified as a factor contributing to children's peer acceptance (Hartup, 1983). Children who have experienced alterations in physical appearance have reported increased levels of teasing, questions and comments from peers, and fewer friendships, due to peer's apprehension and fears over visible abnormalities such as loss of hair or limb (La Greca 1990). BMT is associated with numerous chronic and delayed complications, such as graft versus host disease (GVHD), endocrine abnormalities, and pulmonary complications. These complications have the potential to make enduring changes in observable non social attributes of the child such as general physical appearance (Vanatta et al., 1998). Short stature, dental abnormalities, skin pigmentation changes and permanent hair thinning and loss are relatively common side effects of the treatment.

These effects, in conjunction with ongoing medical interventions may result in restriction in physical activity for BMT survivors. This is likely to have social consequences as it limits the child's ability to participate fully in peer activities (La Greca, 1990).

To date only one study has sought to empirically investigate the impact of peer perceptions of BMT survivor's physical appearance and athletic ability on their social functioning.

Vanatta et al. (1998) compared paediatric BMT survivors to nonchronically ill, same-classroom, same gender comparison peers on measures of social functioning (behavioural reputation and peer acceptance). Results indicated that BMT survivors had fewer friends and were described by peers as being more socially isolated. Importantly they found that changes in appearance and athletic abilities mediated the impact of BMT on these difficulties. These findings are supported by other studies of paediatric chronic illness, whose results combine to suggest that children with conditions that are accompanied by alterations to general appearance and which impose physical limitations have been found to encounter more social difficulties than healthy controls or those with chronic illness alone (La Greca, 1990; Nadeau et al., 2006; Spirito et al., 1990). This hypothesis, however, has yet to be substantiated in the paediatric BMT literature.

#### *Social and cognitive functioning following BMT for congenital immunodeficiency*

To date only one study has sought to investigate the social and cognitive functioning of children treated with BMT only for congenital immunodeficiency (Titman et al., in press). Results indicated significantly high levels of social functioning difficulties compared to normative data. Despite individual variability, as a group these children were experiencing global cognitive difficulties, evidenced by significantly lower IQ scores than the population norm (15 points) and a sibling control group (35 points). Performance within these two domains was significantly correlated, with those children who were experiencing cognitive difficulties also being those who were experiencing problems with social functioning.

### ***The present study***

Employing a cross sectional design, using a cohort of children treated with BMT for congenital immunodeficiency, and a matched control group, the present study seeks to investigate further the difficulties in social competence that has previously been reported in this group of children. It would not be appropriate to compare this cohort of children to normative data and hence a control group is necessary for a number of reasons. First, as a group the children treated for congenital immunodeficiency are of low average intelligence. Thus, a control group matched for IQ is necessary in exploring whether factors other than IQ are related to their social competence. Second, the patients differ from the UK population in terms of the high number of families coming from minority ethnic backgrounds and not speaking English as a first language. The control group is therefore also important in controlling for social and ethnic background.

This study also seeks to investigate potential mechanisms that may underlie difficulties with social competence. It aims to examine executive function ability in this cohort of BMT survivors and explore whether performance in this domain is associated with social competence. In addition, this study also investigates whether social functioning in this particular group of children is related to physical appearance and athletic ability.

The following hypotheses will be tested:

1. Based on the research conducted by Titman et al. (in press) using the same cohort of children, it is predicted that even when controlling for IQ and other social and demographic factors, these children will be experiencing significantly more social difficulties. Peer relationships are hypothesised to be particularly affected.
2. Based on research with adult BMT survivors and observations from assessments carried out with child survivors, it is hypothesised that when controlling for IQ, executive function will be an area of cognition particularly affected in these



children. To fully test this hypothesis, particular domains of executive function, such as planning, working memory, inhibition and sustained attention will be examined separately.

3. Based on previous research with other groups of neurologically compromised children, discussed earlier, it is hypothesised that there will be a positive association between executive function abilities and social functioning in children treated with BMT for congenital immunodeficiency.
4. Based on the findings by Vanatta et al. (1998) it is hypothesised that there will be a positive association between physical appearance and athletic ability and social functioning in this group of children.

## **Method**

### ***Participants***

#### *Patient participants*

All patients aged between eight and 16 years old who had been treated with BMT for a congenital immunodeficiency at one centre (Great Ormond Street Hospital) were eligible for the study, with the exception of those treated for Adenosine Deaminase Deficient Severe Combined Immunodeficiency (ADA SCID) and Chediak Higashi Syndrome. These conditions are characterised by severe cognitive and behavioural difficulties that are markedly different from the rest of the cohort and warrant separate research. Other exclusion criteria included co-morbid chronic medical conditions that would have affected cognitive and/or physical ability to complete the assessments. Of 41 potential participants, 31 completed the assessment; three declined to take part, three were living abroad and four could not be contacted. Sample parameters of the congenital immunodeficiency patients are reported in table 1.

### *Healthy control participants*

Thirty one control group participants, were recruited from two primary schools, one within an inner London borough and one in South Wales; and one secondary school based in South Wales. Exclusion criteria included history of chronic illness and identification as having special educational needs. Participants were matched to the patient group for age, gender, ethnicity and IQ. Given the large number of variables on which to match the groups, it was not possible to use paired matching and group matching was conducted instead. Sample parameters of the control group are reported in table 2.

**Table 1.** *Sample Characteristics of congenital immunodeficiency patients*

Patient Characteristics	Frequency	Percentage
Gender		
Male	20	65
Female	11	35
Ethnicity		
White	21	68
Asian	8	26
Mixed race	2	6
English as first language		
Yes	25	80
No	6	20
Diagnostic category		
Severe Combined Immunodeficiency	18	58
Combined Immunodeficiency - undefined	6	20
Wiscott Aldrich Syndrome	4	13
CGD	1	3
XLP/HLH	1	3
LAD and Glanzmanns	1	3
Conditioning		
Full	18	58
Reduced Intensity	10	33
None	2	6
Data not available	1	3
Age	Mean (S.D.)	Range
Age at BMT (months)	34.7 (39.7)	0 - 141
Age at assessment (months)	151.2 (31.4)	96 - 190
Full Scale IQ score	91.0 (22.6)	41 - 134

*Note:* CGD = Chronic granulomatous disease; XLP = X-linked lymphoproliferative disease; HLH = Haemophagocytic lymphohistiocytosis

**Table 2.** *Sample Characteristics of control group*

Patient Characteristics	Frequency	Percentage
Gender		
Male	20	65
Female	11	35
Ethnicity		
White	23	74
Asian	6	20
Mixed race	2	6
English as first language		
Yes	26	84
No	5	16
Age	Mean (S.D.)	Range
Age at assessment (months)	144.5 (34.6)	96 - 196
Full Scale IQ score	91.9 (16.0)	67 - 135

### ***Procedure***

The families of eligible patient participants were contacted by telephone and given a brief description of the study. Those who indicated an interest in participating were sent an information pack, designed in accordance with the internal Research Ethics Committee and APA guidelines. This consisted of parent/guardian and child information sheets (see Appendix 1), and consent forms (see appendix 2). Families were re-contacted by telephone and a date for the assessment was arranged with those who were willing to participate. Families were given the option of having the assessment conducted at GOSH or at their own homes. This was due to the majority of children living considerable distances from the hospital and only having to attend annual outpatient appointments. The assessment took 1.5 hours to complete.

With regard to the control group, participating schools were given information packs, consisting of parent/guardian and child information sheets (see appendix 3) and consent forms (see appendix 2). In the primary schools, these were distributed to every child aged

eight to 11 years. Due to the large numbers of secondary school aged children, one form class in each year group consisting of children aged 11-16 years were targeted for participation. Those who were willing to participate were asked to return completed parent and child consent forms to the school administrators. Participants were chosen based on age and gender to complete a shortened version of the Wechsler Intelligence Scale for Children, third Edition, (WISC-111; Wechsler, 1991). Those whose IQ best matched those of children within the patient group were then asked to return to complete the full assessment. Both the brief and full assessments were conducted in a quiet room within the participant's school. A match for ethnicity was achieved by recruiting through a primary school with a high proportion of students from minority ethnic backgrounds. Matching for the ethnicity of older patient children (11-16 years) was achieved by recruiting family friends and relatives of the primary school participants.

To aid recruitment, all control participants who consented to take part in the study were entered into a raffle at their school, with the prize for the winner being £40 HMV vouchers.

## ***Measures***

### *Disease and Treatment characteristics*

A patient information database was used to obtain data regarding survivor gender, age at diagnosis and assessment, type of congenital immunodeficiency and type of chemotherapeutic conditioning (none, mini, full).

### *Social and demographic factors*

A social and demographic information sheet was given to families of all participants to collect information regarding ethnicity, first language, parental consanguinity (whether or

not parents were related, e.g. second cousins) and parental occupation (see appendix 4).

Socioeconomic status was rated on a five point scale based on the occupation of the main earner (OPCS, 1991).

### *Social Competence*

*Strengths and Difficulties Questionnaire (SDQ):* Parent, Teacher and Self (if over 11 years) versions (Goodman, 1997).

This is a standardised, brief behavioural screening questionnaire, designed for use with four to 16 year olds. It consists of 25 items, which inquire about psychological attributes, some positive and others negative. The SDQ is scored on a three point likert scale and composed of five scales (each of five items) which yield scores for emotional symptoms, conduct problems, hyperactivity-inattention, peer relationship problems and prosocial behaviour. All but the last scale are summed to generate a Total Difficulties score (0-40). An impact supplement is also included, which if problems are noted, inquires further about chronicity, distress, social impairment and burden to others. The SDQ shows satisfactory reliability with regard to internal consistency (.73); inter-rater reliability (.34); test-retest reliability (.62) (Goodman, 1999; Goodman, Ford et al., 2000b; Goodman, Renfrew et al., 2000a).

### *Social Aptitude Scale (Goodman, 2000)*

The Social Aptitude Scale (SAS) is part of the Development and Well Being Assessment (DAWBA, Goodman 2000). The DAWBA is designed to generate ICD 10 and DSM V psychiatric diagnoses on five to 17 year olds and has been found to make excellent discrimination between community and clinic samples (Goodman et al., 2000). Linked to the SDQ, the SAS is reported to be more sensitive to detecting subtle social difficulties. It is scored on a five point likert scale and comprises a brief description of 10 social situations.

The informant is asked to rate the child in terms of how he/she compares with other children of his/her age.

*Vineland Adaptive Behaviour Scales – Survey Edition: Socialisation domain (VABS: Sparrow et al., 1984)*

The VABS is the best researched and most widely used measure of the adaptive maturity of the individual from birth to adulthood. It is developmentally sensitive, providing different items for different age ranges. The socialisation scale enquires into the participant's habitual observable social behaviour, as rated by parents. The parent was asked to read each phrase and mark the response that best described their child's behavior. The response reflects how often the child performs the behavior without help, when the behavior is needed. The socialisation domain shows satisfactory reliability with regard to internal consistency (.86); test-retest reliability (.81) and inter-rater reliability (.62) (Sparrow et al., 1984).

*Matson Evaluation of Social Skills with Youngsters (MESSY; Matson, 1981) teacher and self versions*

The MESSY provides a 64 item Teacher Rating and a 62 item Self Rating Questionnaire. All MESSY items measure social skills and refer to observable social behavior, rather than to personality traits. Each item is rated on a five point likert scale. Both the Teacher and the Self Rating versions yield a total score, which is in the direction of negative social skills, with high scores indicating poor social skills and low scores indicating good social skills. Both the Teacher and Self Rating Version meet the criterion of .50 test-retest reliability and show a high degree of internal reliability, with Guttman split-half reliability being .87 for the Teacher Version and .78 for the Self Rating version (Matson et al., 1981).

### *Cognitive Function (IQ)*

#### *Wechsler Intelligence Scale for Children, Third UK Edition (WISC-III; Wechsler, 1991)*

IQ data was already available for the patient group, who had 2 years previously, been assessed with the full version of this measure. The control group were assessed using a shortened format, consisting of two verbal subtests: Vocabulary and Similarities and two performance subtests: Block Design and Picture Completion. Full Scale IQ score estimates for each participant were obtained by prorating the scale scores achieved for these tests.

### *Executive Function*

#### *Maudsley Attention and Suppression Response Task Battery (MARS) (Rubia et al., 2007)*

Three computer based tests, described below, that have been developed to avoid the confounds of the more traditional tests of executive function, were used. They are currently undergoing standardisation and have been used extensively on paediatric ADHD populations, where, as a battery, they have showed a 76% correct discrimination of cases and controls (Rubia et al., 2007).

#### *Go-No-Go task (Rubia et al., 2007)*

This is a selective motor response inhibition task, where a motor response has to be either executed or not. The test is divided into two sub-tests, blocked for a left and a right-handed response. Green space ships each pointing to the left in one subtest and the right in the other subtest, briefly appear in the middle of the screen and participants have to make a button press response. In 26.3% of trials, green enemy planets briefly appear in the middle of the screen instead of the space ships and participants have to inhibit their motor response. There are 95 trials for each subtest, 70 Go trials and 25 No-Go trials. The dependent variable of the task is the number of commission errors to the No-Go stimuli. Total task duration is five minutes (see appendix 5 for an illustration of this task's visual stimuli)

### *Switch Task (Rubia et al., 2007)*

This is a cognitive inhibition task, which primarily investigates pure attentional switching between two different spatial dimensions. In addition, it provides a measure of sustained attention. It has been found to avoid the working memory confounds of other switch tasks, such as the Wisconsin Card Sorting Task (Smith et al., 2004). Participants are presented with a grid divided into four squares, in the centre of which is a double-headed arrow. A red dot then appears in any of the four squares on the grid. A horizontally pointing double-headed arrow indicates that the participant had to decide whether the circle was in either of the two left or the two right squares of the grid, by pressing the left or right button. After 1600ms presentation time, there is a blank screen for 800ms, during which participants make their response. This presentation is repeated for several repeat trials. These repeat trials are then followed by a switch trial, in which the arrow changes to a vertical position and the participant has to indicate whether the circle is in either of the upper two or lower two squares of the grid, by pressing the top or bottom button. Again, this instruction is maintained for several repeat trials, followed by another switch trial, in which the arrow changes back to a horizontal position, and so on. This pattern continues for 128 trials with high frequency repeat trials, interspersed with low frequency repeat trials. There is a minimum of two repeat trials before every switch trial. The dependent variables are the Switch effect, which measures ability to switch response set (the mean reaction time to repeat trials subtracted from the mean reaction time to switch trials) and the error effect, which measures sustained attention (total number of error made across both repeat and switch trials). Task duration is five minutes. (See appendix 6 for an illustration of this task's visual stimuli).



*Rewarded-CPT task (Rubia et al., 2007)*

This is a test of sustained attention. A string of letters (A-L from the alphabet) are presented to the participant with a trial time of 1 second. Participants are required to ignore all letters except for the target letters. Target letters are an A followed by an X and an A followed by an O. Participants can see how well they are doing at detecting the target letters by visually displayed coloured bars on the screen, one for each target pair. The dependent variable is the number of commission errors, i.e. false hits to non-target items. Total task duration is eight minutes. (See appendix 7 for an illustration of this task's visual stimuli).

*Tower (NEPSY: A Developmental Neuropsychological Assessment; Korkman, Kirk & Kemp, 1997)*

The tower subtest of the NEPSY assesses the executive functions of planning, monitoring, self-regulation and problem solving. It requires the participant to move three coloured balls to target positions on three pegs in a prescribed number of moves under time pressure. There are also a number of rules to which the participant must adhere on this task. There are 20 items in total, which increase in difficulty. The time limit is set at 30 seconds for the first four items, followed by 45 seconds for the remaining 16. The task is discontinued following four failures. This test shows good internal reliability (.82).

*Digit Span (WISC-111: Weschler Intelligence Scale for Children – Third Edition: Weschler, 1991)*

This is a test of working memory. It involves the experimenter reading aloud increasingly long sequences of numbers, which participants are required to repeat. The first task 'Forward Digit Span', involves participants repeating the numbers in the same order as the experimenter read them. The second, more challenging task 'Backwards Digit Span' requires participants to recite the numbers in reverse order. This test was administered and scale scores generated, as described in the WISC-III manual.

*Physical appearance and athletic ability (completed by the BMT group only)*

*The Self-Perception Profile for Children and for Adolescents (Self-PP; Harter, 1985, 1986)*

The subscales of physical appearance and athletic ability were the only domains of interest to this study. To reduce socially desirable responding, participants are asked to rate themselves relative to 'some children...or other children' and decide how much they are like one or the other group. The child version (eight to 12 years) and adolescent version (12-18) comprise six and five items respectively for each domain. UK studies have confirmed the high internal reliability of the Self-PP subscales (John, 1997).

*Clinicians rating of BMT children's physical appearance*

A brief Likert Scale was developed to assess clinician's ratings of children's physical appearance. Participants were rated by one clinician (Consultant Clinical Psychologist) and scores corroborated by another clinician (Consultant Immunologist). Each participant was given a score of between one and five (1 = no sign of alterations to physical appearance; 2 = alterations in physical appearance only noticeable to the child and family; 3 = subtle alterations in physical appearance noticeable to others outside the family but not disfiguring; 4 = moderate alterations in physical appearance, immediately noticeable by others; 5 = severe alterations in physical appearance, constituting disfigurement).

### ***Ethical considerations***

The proposal was reviewed by the Great Ormond Street Hospital for Children NHS Trust/Institute of Child Health Research Ethics Committee. A copy of the approval letter is shown in Appendix 8.

### ***Sample Size Estimation and calculation of Statistical Power***

The effect size estimate (Cohen's *d*; Cohen, 1988) was based on previous studies that examined global cognitive functioning and social competence in children treated with BMT for congenital immunodeficiency (Titman et al., in press) and other conditions (Vanatta et al., 1998). An effect size of .8 and *p* value of <.05 were selected to identify the number of participants necessary to find significant differences in key outcome variables. The minimum aggregate sample size estimated was 30 participants.

### ***Data Analysis***

12 outlying scores (five from the Congenital Immunodeficiency group; seven from the control group) showing extreme scores (deviating more than three times the standard deviation of the group mean) were excluded from the analysis. One score from five children in the congenital immunodeficiency group was excluded, from the following measures: Parent SDQ pro social (N=1); Parent SDQ impact (N=1); VABS (N=1); Teacher rated MESSY (N=1); NEPSY tower (N=1). One score from seven control participants was excluded from the following measures: Parent SDQ impact (N=2); Teacher SDQ impact (N=2); Teacher SDQ pro social (N=1); Teacher SDQ peer (N=1); commission errors-reward CPT task (N=1).

The data fulfilled the assumptions necessary for analysis using parametric statistics. To test for between group differences in social competence, independent t. tests were conducted on the following dependent variables: SDQ peer, pro-social and impact domains (parent, teacher, self), VABS total score (parent), SAS (parent), and MESSY total score (teacher, self).

With the exception of Digit Span, the tests measuring executive function were not age standardised. Exploratory analysis using Pearson's Correlation Analyses revealed a significant correlation between age and scores on these measures for both groups of

children. To test for between group differences on measures of executive function, analysis of covariance with age entered as a covariate were employed.

Pearson's Correlation analyses were used to investigate the association between the social competence dependent variables and scores on the measures of executive function.

Pearson's Correlation Analyses were also used to investigate the relationship between the social competence dependent variables and scores on measures of physical appearance and athletic ability (Harter Self Perception Profile; Clinicians rating of overall physical appearance).

Exploratory analyses revealed no significant effects of gender with regard to any of the variables studied. Thus, the effect of gender on outcome measures was not included in the analysis.

Effect sizes were calculated for all dependent measure comparisons using Cohen's *d* (Cohen, 1988).

In order to control for multiple testing, significance levels were adjusted according to the False Discovery Rates (Benjamini & Hochberg, 1995).

## **Results**

Independent t. tests showed no significant group differences in age ( $t(60) = .795, p = .430$ ) or IQ ( $t(54) = .175, p = .862$ ). There was no significant relationship between ethnicity and group ( $X^2(6) = 3.914, p = .688$ ) or between SES and group (Mann Whitney  $U = 396.000, p = .215$ ). Thus it can be assumed that the groups are no significantly different to each other with regard to any of the key matching variables.

### ***Hypothesis 1: Group differences in social competence***

The results for the social competence dependent variables are shown in table 3.

### *SDQ data*

Regarding the 'peer' domain of the SDQ, children in the congenital immunodeficiency group were rated as experiencing significantly more difficulties with peer relationships than children in the control group by both parents ( $t(45) = 2.43, p = .019$ ) and teachers ( $t(34) = 2.40, p = .022$ ) but not by themselves ( $t(32) = -.14, p = .889$ ). Furthermore, the impact of these difficulties in terms of distress to the child, social impairment and effect on classroom learning was rated as significantly greater for congenital immunodeficiency children, compared to controls by parents ( $t(27) = 3.87, p = .001$ ) and teachers ( $t(27) = 2.87, p = .008$ ) but again not by themselves ( $t(32) = .64, p = .530$ ). Teachers also rated congenital immunodeficiency children as exhibiting significantly fewer pro-social behaviours compared to control children ( $t(52) = -3.25, p = .002$ ). This finding was not corroborated by parents ( $t(54) = -1.00, p = .321$ ) or self report ( $t(32) = -.47, p = .850$ ).

### *VABS and SAS data*

Consistent with the SDQ data, SAS scores indicated that children with congenital immunodeficiency were rated by their parents as comparing significantly less favourably to children their own age in social situations, than were children in the control group ( $t(49) = -2.22, p = .031$ ). Congenital immunodeficiency children were also rated by their parents on the VABS as demonstrating fewer age appropriate social behaviours than were controls, however, this finding was no longer significant once the p. value had been corrected for multiple testing ( $t(45) = 2.05, p = .046$ ).

### *MESSY data*

In contrast to the above findings, scores for the MESSY questionnaire showed no significant group differences in social skills when rated by teachers ( $t(53) = -.03, p = .976$ ) or children themselves ( $t(58) = .35, p = .731$ ).

These data provide partial support for the hypothesis that children treated with BMT for congenital immunodeficiency would be functioning less well socially than matched controls. Good support, however, is provided for the idea that within the domain of social competence, peer relationships would be a particular area of difficulty for children treated with BMT for congenital immunodeficiency.

**Table 3:** *t. tests for the social functioning variables by group*

variable	Patient mean (SD)	Control mean (SD)	t	p-value	Effect size <i>d</i>
<b>Parent data</b>					
SDQ peer	2.43 (2.08)	1.31 (1.29)	2.43	.019*	0.7
SDQ Pro social	8.74 (1.40)	9.07 (1.03)	-1.00	.321	0.3
SDQ Impact	1.64 (2.13)	0.07 (0.27)	3.87	.001*	0.9
SAS	21.75 (8.22)	26.00 (6.01)	-2.22	.031*	0.6
VABS (total)	124.61 (14.41)	131.14 (8.90)	2.05	.046	0.6
<b>Teacher data</b>					
SDQ Peer	2.15 (2.58)	0.86 (1.08)	2.40	.022*	0.7
SDQ Pro Social	7.30 (1.98)	8.89 (1.66)	-3.25	.002*	0.9
SDQ Impact	0.74 (1.26)	0.04 (0.19)	2.87	.008*	0.9
MESSY (total)	112.96 (19.34)	113.17(30.28)	-.03	.731	0.01
<b>Self data</b>					
SDQ Peer	1.85 (1.63)	1.93 (1.54)	-.14	.889	0.05
SDQ Pro social	7.80 (1.00)	8.00 (1.47)	-.47	.640	0.2
SDQ Impact	0.55 (1.00)	0.36 (1.54)	.64	.529	0.1
MESSY (total)	116.76 (20.54)	115.03(10.23)	.35	.731	0.1

Note. SDQ: scores for the peer, pro-social and impact domains of the Strengths and Difficulties Questionnaire (Goodman., 1998); SAS: scores for the Social Aptitude Scale (Goodman., 2000); MESSY: scores for the Matson Evaluation of Social Skills in Youngsters (Matson et al., 1981); N ranged from 27-29 for the congenital immunodeficiency group and from 27 to 31 for the control group across the above variables. \* t. test is significant at alpha <.05 after correction for multiple testing using False Discovery Rate of Benjamini & Hochberg (1995).

### ***Hypothesis 2: Group differences in executive function***

The results for the executive function dependent variables are shown in table 4. The only significant group difference was found for the 'error effect' dependent variable of the Switch task. Whilst the congenital immunodeficiency group did not make significantly more errors in the switch condition compared to the repeat condition of the switch task, compared to the control group they made significantly more errors overall

( $F(1, 58) = 7.129, p = .010$ ) with a medium to large effect size (.6). There were no significant differences between the groups on all other measures of executive function.

These findings provide only limited support for the hypothesis that executive functions would be a particular area of cognition affected in children treated with BMT for congenital immunodeficiency, compared to IQ matched controls. No significant group differences were found on tasks examining planning, inhibition, ability to switch response set and working memory. However, a significant group difference was found on a measure of sustained attention.

***Hypothesis 3: Association between social competence and executive function in children treated with BMT for congenital immunodeficiency.***

The results of the Pearson's Correlation Analyses between social competence and executive function are shown in table 5.

With the exception of Digit Span, there were no significant correlations between measures of social competence and performance on tests of executive function. Performance on Digit Span correlated significantly with parent ratings of social competence:

SDQ peer ( $r = -.4, P = .023$ ); VABS ( $r = .4, P = .018$ ); SAS ( $r = .5, P = .004$ ).

These data provide very limited support for the hypothesis that executive function ability may be associated with social functioning in children treated with BMT for congenital immunodeficiency.

**Table 4:** ANCOVAS for the executive function variables by group, with age as a covariate

variable	Patient mean (SD)	Control mean (SD)	F	p-value	Effect size <i>d</i>
Digit span	7.97 (3.14)	9.13 (2.92)	2.03	.160	0.4
NEPSY tower	12.90 (2.22)	13.39 (2.16)	2.24	.140	0.2
Probability of inhibition (go-no-go task)	80.53 (11.47)	79.23 (14.75)	.00	.991	0.1
Reaction time cost (switch)	50.78 (57.02)	53.66 (52.48)	.00	.975	0.05
Error effect (switch task)	5.47 (7.80)	1.85 (4.83)	7.13	.010*	0.6
Commission errors (Reward CPT task)	3.04 (2.43)	3.77 (2.78)	.54	.465	0.3

Note: N ranged from 29-31 for the congenital immunodeficiency group and from 30-31 for the control group across the above variables. \* t. test is significant at  $p < .05$ .

**Table 5:** Correlations between the social competence and executive function variables for the congenital immunodeficiency group

		Digit Span	Tower	Probability of inhibition	Error effect	Commission errors
Parent data						
PSDQ peer	r	-.43	-.01	.06	-.02	.01
	p	.02*	.98	.78	.91	.94
PSDQ prosocial	r	.00	.04	.07	-2.6	.15
	p	.99	.85	.71	.18	.47
PSDQ impact	r	.33	.05	-.02	-.02	.26
	p	.09	.79	.94	.94	.19
SAS	r	.53	-.01	.20	-.08	-.02
	p	.004*	.96	.33	.71	.94
VABS total	r	.45	-.01	-.06	-.14	-.10
	p	.018*	.96	.77	.47	.63
Teacher data						
TSDQ peer	r	-.14	.26	.13	-.18	-.10
	p	.48	.20	.53	.37	.62
TSDQ prosocial	r	.15	-.11	.07	-.06	.21
	p	.45	.59	.73	.79	.31
TSDQ impact	r	-.28	.25	.23	-.16	-.19
	p	.16	.21	.26	.43	.36
MESSY	r	.10	-.11	.03	-.04	.09
	p	.64	.60	.91	.85	.68

Note. Pearson Correlation coefficients (r) across variables and corresponding corrected p. Values; SDQ: scores for the peer, pro-social and impact domains of the Strengths and Difficulties Questionnaire (Goodman., 1998); SAS: scores for the Social Aptitude Scale (Goodman., 2000); MESSY: scores for the Matson Evaluation of Social Skills in Youngsters (Matson et al., 1981). N ranged from 26-30. \* correlation is significant at  $p < .05$  after correction for multiple testing using False Discovery Rate of Benjamini & Hochberg (1995).



***Hypothesis 4: Association between social competence and physical appearance in children treated with BMT for congenital immunodeficiency.***

Results of the Pearson's Correlation Analyses between social competence and physical appearance/athletic ability are shown in table 6.

First, as rated by the children themselves, athletic ability and physical appearance are significantly correlated ( $r = .5$ ,  $p = .002$ ).

***Athletic ability and social competence***

Athletic ability was significantly correlated with the impact domain of the teacher rated SDQ ( $r = -.6$ ,  $p = .001$ ). Athletic ability was also correlated with scores on the parent rated VABS questionnaire, although this finding is no longer significant after correction for multiple testing. In addition, there is a trend towards an association between athletic ability and the peer domain of the teacher rated SDQ, with a small effect size ( $-.4$ ), although this does not reach statistical significance. Athletic ability was not found to be significantly correlated with any other measures of social competence.

***Physical appearance and social competence***

Physical appearance, as rated by the children themselves, using the Harter Self Perception Profile was not significantly correlated with any of the social competence dependent variables. Self-rated physical appearance was also not significantly correlated with the clinician's rating of physical appearance ( $r = -.1$ ,  $p = .790$ ). Clinician's rating of physical appearance was not significantly correlated with any parent rated measures of social competence. In contrast, clinician's rating of physical appearance was significantly correlated with all teacher rated measures of social competence: SDQ peer ( $r = .6$ ,  $P = .001$ ), pro-social ( $r = -.4$ ,  $P = .039$ ) and impact ( $r = .6$ ,  $P = .002$ ); MESSY ( $r = .5$ ,  $P = .014$ ).

These data provide partial support for the hypothesis that social competence would be associated with physical appearance and athletic ability in children treated with BMT for congenital immunodeficiency.

**Table 6:** *Correlations between the social competence and physical appearance/athletic ability variables for the congenital immunodeficiency group*

	Harter athletic competence	Harter physical appearance	Clinician rated physical appearance
Harter physical appearance	.5 .002*		
Clinician rated physical appearance	-.1 .592	-.1 .790	
Parent data			
PSDQ peer	-.2 .326	-.1 .468	.1 .487
PSDQ prosocial	.2 .394	.2 .423	.0 .857
PSDQ impact	-.3 .096	-.2 .334	.1 .632
SAS	.3 .133	.0 .967	-.3 .095
VABS	.5 .014	.3 .153	-.4 .057
Teacher data			
TSDQ peer	-.4 .053	-.2 .374	.6 .001*
TSDQ prosocial	.2 .438	-.1 .781	.4 .039*
TSDQ impact	-.6 .001*	-.3 .144	.6 .002*
MESSY	.2 .414	.0 .899	.5 .014*

Note. Pearson Correlation coefficients (r) across variables and corresponding corrected p. Values; SDQ: scores for the peer, pro-social and impact domains of the Strengths and Difficulties Questionnaire (Goodman., 1998); SAS: scores for the Social Aptitude Scale (Goodman., 2000); MESSY: scores for the Matson Evaluation of Social Skills in Youngsters (Matson et al., 1981). N ranged from 26-31. \* correlation is significant at  $p < .05$  after correction for multiple testing using False Discovery Rate of Benjamini & Hochberg (1995).

## Discussion

This study examined the social functioning of children treated with BMT for congenital immunodeficiency. It extended previous work in several ways. First, it represents one of the first studies within paediatric BMT research to use a homogenous diagnostic population of children which enables disease specific processes to be explored. Second, and again relatively rare in the BMT literature, a control group were employed, matched for a number of key demographic variables and for IQ. Matching for IQ was essential in controlling for the possibility that the social functioning difficulties previously identified in this cohort of children were simply a product of lower IQ. The current study then sought to investigate the mechanisms that may be underpinning these difficulties with social competence. A hypothesised association between executive function abilities and social competence was explored. In addition, this study sought to investigate the relationship between non social attributes of physical appearance and athletic ability and social competence in this cohort of children.

### *Social Competence*

Overall, the results supported the hypothesis that even when controlling for IQ and key demographic variables, children treated with BMT for congenital immunodeficiency would be experiencing significant difficulties with social functioning. Parent reports of social competence were similar to that of teachers. Parent and teacher information regarding social functioning is often found to be inconsistent, given that parents primarily observe their children at home, rather than during direct interactions with peers (Reiter-Purtill et al., 2003). Thus, the agreement of both parents and teachers with regard to social difficulties in these children is noteworthy. Combined with the large effect sizes obtained, it suggests that the difficulties in social competence represent very real problems that occur across settings.

The congenital immunodeficiency group were described as experiencing significantly more difficulties with peer relationships than were controls (e.g. having fewer friends; being less accepted by peers and tending to be solitary and play alone, as assessed by the SDQ). They were compared less favourably to children of their own age in social situations than were control participants. Such situations included being easy to chat with, being able to read between the lines of what people say and being aware of what is and isn't appropriate in different social situations. In addition, both parents and teachers reported these difficulties as having a significant impact on the children, in terms of distress caused to both child and family and on the children's ability to function effectively in home, classroom and leisure activities.

The only difference between parent and teacher reports concerned the assessment of pro-social behaviours. Teachers, but not parents, rated children in the congenital immunodeficiency group as exhibiting significantly fewer pro-social behaviours compared to controls. The questions used to assess pro-social behaviour include 'shares readily with other children', 'helpful if someone is hurt, upset or feeling ill', 'often volunteers to help others'. It could tentatively be suggested that scores for these items may reflect lower levels of self confidence in this group of children when in classroom based social situations. This would be consistent with previous findings of lower levels of self esteem and confidence in children post BMT (Phipps et al., 1995).

In contrast to both parent and teacher data, there were no group differences in self ratings of social competence. This is consistent with findings from previous studies of paediatric BMT (Vanatta et al., 1998) and cancer survivors (Canning et al., 1992). Such studies have described these populations of children as manifesting an exaggerated use of denial and a need to present themselves in a good light when completing such measures. Thus, they suggest that the children's own accounts of their functioning should not be taken at face

value. Alternatively, having experienced and survived a chronic illness and its treatment, children in the congenital immunodeficiency group may be using different benchmarks than healthy controls to assess themselves against.

*Mechanisms underlying social difficulties: Executive function*

Based on suggestions in the literature, this study sought to investigate first, whether executive function was an area of cognitive ability affected in children treated with BMT for congenital immunodeficiency; and second, whether executive dysfunction was a mechanism underlying the difficulties with social competence experienced by this group of children.

With regard to the first aim, the results largely did not support the hypothesis of impaired executive function ability in children treated for congenital immunodeficiency compared to controls. The exception was on a task of sustained attention where children in the congenital immunodeficiency group performed significantly worse than children in the control group. This finding supports previous research in which paediatric BMT survivors have been reported by teachers as having poor concentration and a short attention span (Arvidson et al., 1999).

The only domain of executive function that was significantly correlated with measures of social competence was the Digit Span test of working memory. However, as would be expected, exploratory analyses revealed a strong significant correlation between Digit Span and IQ in this group of children. Thus, the association between performance on Digit Span and social competence likely reflects more the relationship between IQ and social functioning that exists both generally (Cicchetti & Cohen, 1995) and in this group of children (Titman et al., in press). This suggestion is supported by the fact that the association between scores for Digit Span and social competence was not specific to the

congenital immunodeficiency group. Similar results, although not reported, were found for the control group.

This general lack of a relationship between executive function and social competence is in contrast to findings from studies of other groups of neurologically compromised children (Fisher et al., 2005; Lopez et al., 2005; Seguin et al., 1999). A tentative suggestion to explain the lack of a significant association between these domains is that the measures used may not reflect the children's ability to access and utilise these executive function competencies in everyday social interactions. This may be due to the differences between the relatively controlled testing environment and the more complex social information processing situations in the real world. The findings of one study should never be taken as incontrovertible evidence for or against any position. This is the first study to investigate executive function in this group of children. Thus, further research, using perhaps more ecologically valid measures of executive function, is needed before it can be concluded with more certainty that this area of cognition is not related to social competence in this group of children.

Investigation into other cognitive processes that may underlie the problems with social competence in these children is also needed. In this cohort of children, BMT typically occurs during a critical period of cognitive and social development. Normally, across the second year of life children are becoming increasingly explorative and there is a transition from independent activities to social relationships. Theory of Mind (TOM), an important foundation for children's social and communicative functioning, develops. Considered a component within the broader cognitive domain of executive function, TOM concerns the ability to understand that others have beliefs, desires and intentions different to one's own and hence make behavioural predictions about how they will act (Perner & Lang, 1999). The development of TOM is influenced by a number of factors including attachment, parenting

styles and sibling relationships and is thought to have been accomplished by four to five years of age (Riggs et al., 2006). Notably the majority of children with congenital immunodeficiency are either undergoing or have just undergone BMT at this age. The considerable disruptions to family functioning and restrictions placed on social interactions during this critical period may result in limited opportunities to learn from social interactions and modify or improve skills that may already be limited or under-developed as a result of illness. An interesting avenue for future research into the social difficulties experienced by this group of children could be to assess their TOM abilities, using a social information processing framework.

*Mechanisms underlying social difficulties: Physical appearance and athletic ability*

The non-social attributes of physical appearance and athletic ability, as rated by the children were significantly correlated. This suggests that they are not mutually exclusive and that children whose physical appearance is altered as a result of BMT are also likely to experience difficulties with athletic activities. This makes sense, given that physical deformities that can occur as a result of the BMT process, such as stunted growth affect both physical appearance and athletic ability. Additionally, altered physical appearance may affect children's confidence in becoming involved in peer related athletic activities.

The discrepancy between children's rating of their own physical appearance and the clinician's rating of their appearance was striking. However, the child measure and clinician's measure assess very different things: The former, the children's perceptions of satisfaction with their general physical appearance; the latter specifically addressing changes as a result of the BMT procedure. The discrepancy might therefore reflect these differences in measurement. In this respect, it may have been interesting to have the children also complete the clinician's scale. Second, the Harter Self Perception Profiles

(Harter, 1985, 1986) may not be sensitive enough to changes in physical appearance that reflect the children's experience.

Physical appearance as rated by the children was not significantly correlated with any of the social competence measures. The clinician's rating of physical appearance, however, correlated significantly with all four teacher rated measures of social competence. The fact that this finding comes from two separate sources of information, outside of the immediate family system, is noteworthy and adds to its validity. This finding supports previous research which has found that children whose physical appearance is affected by the BMT process do more poorly with regard to social functioning than those whose appearance is not affected (Vanatta et al., 1998). It is also consistent with other studies that have reported an association between physical appearance and social competence in both the general population (Hartup, 1983) and in samples of children with chronic illness (La Greca, 1990; Nadeau et al., 2006; Spirito et al., 1990).

This finding has clear clinical implications. BMT survivors whose physical appearance is altered, or whose chronic problems impair athletic ability are at higher risk for problems with peer relationships and social functioning. Attention to these variables in the post transplant period could help to identify which children may need psychological services once they have started to reintegrate into social situations.

As Vanatta et al. (1998) previously suggested, investigation is needed into how these children cope with and respond to peers about changes in their appearance and physical abilities. In addition, research into whether interventions to teach skills in this area could promote social competence for BMT survivors is warranted.



### *Methodological limitations*

Important associations between social functioning difficulties and potential underlying mechanisms were identified in this cohort of paediatric BMT survivors. However, the cross-sectional design means that it is not possible to make causal inferences. Well designed longitudinal studies are needed in order to ascertain directions of causality.

Whilst this study sought to improve its methodological quality by collecting data from multiple informants, the lack of appropriate measures of social competence for use with children who have experienced chronic illness was problematic. Other studies investigating similar constructs in chronically ill paediatric populations have reported experiencing a similar difficulty (Barrera et al., 2000; Spirito et al., 1990). It was not possible to thoroughly examine very specific hypotheses about peer relationship difficulties. With the exception of peer nominations, which were outside the scope of this study, no suitable measures specifically pertaining to peer relationships could be found. The SDQ provided the most appropriate measure, however, it's 'peer' and 'pro-social' domains consist of only five items each, which limits ability to make strong conclusions.

Second, with regard to executive function, a number of non-standardised computer-based measures were used. These were chosen because they have been developed to tap specific domains of executive function ability and avoid the confounds of some of the more traditional tests. However, their use may have affected the results and is a limitation.

A further limitation concerns the use of only one experimenter, not blind to the study hypotheses. This introduces the possibility of experimenter bias influencing the results obtained to fit with the predictions made. Whilst measures were taken to avoid this, such as using an additional marker for a subset of score sheets, it still represents a serious limitation.

## *Conclusion*

In conclusion, the results of this study suggest that children treated with BMT for congenital immunodeficiency are experiencing significant difficulties in social functioning, not solely accounted for by below average intelligence. In addition, these difficulties persist a long time after transplant, suggesting that they are not just representative of short term struggles with reintegration into social situations after BMT. In terms of underlying mechanisms that have been studied, most evidence currently points towards the non-social attributes of altered physical appearance and athletic ability. However, the cognitive and social difficulties experienced by these children are not unrelated and more work is needed to identify which particular cognitive processes may be related to social competence in this cohort of children.

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## **‘Part 3: Critical Appraisal’**

## **Evaluation of the current thesis**

Paediatric bone marrow transplant (BMT) is one of the most impressive medical success stories of the latter half of the twentieth century (Phipps, 2005). Until the mid 1960's, chronic haematological and oncological illnesses such as leukaemia and congenital immunodeficiency were almost always fatal. Rapid and dramatic medical advances, and particularly the introduction and success of BMT has resulted in increasing numbers of long term survivors of such previously fatal chronic illnesses. This rapidity in medical advances, however, has presented a challenge for psychosocial research within this area, that of simply keeping up. Psychosocial research takes time to develop and having a moving target does not help (Phipps, 2005).

To stay in line with the medical progress, researchers have increasingly sought to investigate the long term psychological (cognitive and psychosocial) outcomes for children, treated with bone marrow transplant (BMT). The aims of these studies have been similar and can be thought of as three main stages through which to progress:

1. To identify potential psychological difficulties and describe the nature of these
2. To determine the mechanisms that might underlie the difficulties found and hence explain them
3. To use the information gained to provide support and targeted intervention to those children identified as at risk or who are already experiencing difficulties and their families.

Conducting empirical research with chronically ill paediatric populations such as those treated with BMT is incredibly complex. Progress to date has been hindered by factors affecting the methodological quality of studies, such as small and extremely heterogeneous samples with regard to diagnoses, treatment regimes and age at both transplant and assessment. Consequently, findings regarding the presence of cognitive and/or

psychosocial difficulties have been inconsistent with considerable variability being reported both within and across studies. Despite these inconsistencies, it is apparent that a proportion of children do seem to experience significant cognitive and/or psychosocial difficulties following BMT. However, because of the methodological constraints, determining which children are experiencing what problems and what the mechanisms underlying these might be has not been possible in the majority of studies. This is worrying, given the aforementioned medical advances that have resulted in increasing numbers of children being treated with and surviving BMT.

To make further progress towards the ultimate goal of developing evidence based interventions for those children identified as being at risk for or currently experiencing difficulties, BMT research needs to progress from being predominantly descriptive to being more explanatory. The increase in the number of long term survivors of paediatric BMT should now make it more possible to do this. Future studies should be able to narrow their exclusion criteria and separately research different diagnostic groups without compromising statistical power.

Titman et al. (in press) were the first to empirically investigate cognitive and psychosocial difficulties in a homogenous cohort of children treated with BMT for congenital immunodeficiencies. Studying a large, homogenous population afforded a number of benefits, including an understanding of the nature of the difficulties experienced by some of the children and the identification of risk and resilience factors specific to this diagnostic group.

The empirical research described in the current thesis aimed to progress the field further by investigating the mechanisms that might underlie the difficulties with social functioning that were identified by Titman et al. (in press) in children treated with BMT for congenital immunodeficiency. In doing so, a main objective was to make progress towards developing

a theoretical and conceptual framework specific to this group of children that could be used clinically to help guide assessment and intervention. This is discussed in more detail later in this paper, where we consider ‘what next?’ However, before focussing on potential future developments, a critical appraisal of the current research study is warranted. This takes the form of identifying factors that may have influenced the current findings, considering their implications and exploring ways of improving the research methodology in this field.

*Small sample sizes – could multisite research be the way forward?*

Conducting a study using a homogenous sample of children who have survived a rare chronic illness and aggressive treatment regime has some obvious limitations. First, the number of potential participants from Great Ormond Street Hospital, one of the only two centres in the UK who provide treatment for children with a congenital immunodeficiency, was just 41. Thirty one children (75%) agreed to take part in the study. Before thinking more scientifically about how this number fits with what is required to find a medium effect size, it should be noted that a 75 percent participation rate in clinical research is considerable. The commitment of these families to work alongside professionals to help expand and deepen our knowledge of the long term psychological outcome for both current and future long term survivors of paediatric BMT was striking. Going back to the science, however, whilst the number of participants conformed to the sample size of 30 to 40 estimated by the power analysis, it is at the lower end of the range. This means that small but clinically significant effects may have been missed.

Obtaining a large sample of this cohort of children is a challenge and may require a multisite approach. Combining forces with Newcastle General Hospital, the other UK site for treatment of children with congenital immunodeficiency, could be beneficial for a number of reasons. First, it would allow for larger sample sizes and hence increase the reliability and validity of the empirical research; Second, it would promote the sharing of

knowledge, with professionals working together to establish evidence-based theoretical frameworks that can guide psychological assessment and interventions for these particular children and their families. Having a larger cohort from which to sample participants would also ensure that the same children and families are not being put under increasing pressure to participate in more and more studies. Children surviving BMT have been described as feeling less competent and confident than their classmates with regard to both intellectual activities and social functioning (Phipps et al., 1995). Over-researching these children and particularly focussing on problems could potentially have the undesired effect of accentuating these feelings of being different to their 'healthy' peers.

Setting up multisite research, however, is a challenging process, requiring time, money and dedication. Researchers need to agree upon the areas of study and the methods used to study them. In addition, those collecting the data need to be following the same procedures to ensure comparability of findings. Most Psychologists are not sufficiently trained in specific skills and knowledge necessary to conduct these studies (Armstrong & Drotar, 2000). These challenges however, are not insurmountable and consideration does need to be given to developing multisite research studies in this area. Indeed, the paediatric BMT medical research studies are now all done as part of a Europe wide collaboration.

*Is it appropriate to apply a psychopathology framework to the understanding of individuals' psychological adjustment following chronic illness and its treatment?*

Increasingly, the literature suggests that it may not be appropriate to attempt to conceptualise children's psychological adjustment following aversive medical conditions and procedures using a psychopathology framework (Barrera et al., 2000). In particular, it has been suggested that traditional measures of psychological maladjustment may be ineffective and/or insufficiently sensitive in the assessment of social, emotional and

behavioural changes related to medical conditions (Spirito et al., 1990). After much investigation into methods of assessing social functioning, a combination of standardised measures was selected for the current thesis. However, it seemed that none really adequately captured the specific difficulties with regard to social skills and peer relationships that we observe clinically with these children. Of course, there are more sophisticated measures of social behaviour such as peer nominations used in classroom comparison designs (e.g. Vanatta et al., 1998), however, these are too time intensive to be used in most research studies and in routine clinical work. Given the well established relationship between social functioning and later emotional and psychological adjustment in the general population (Parker & Asher, 1987), together with the well documented increased risk for problems with social functioning in children with chronic illness (La Greca, 1990; Nadeau & Tessier, 2006; Reiter-Purtill et al., 2003; Vanatta et al., 1998) it would seem essential that more suitable measures specific to these children are developed and standardised.

*Is it fair to compare these children to 'healthy' control participants?*

The current thesis compared children treated with BMT for congenital immunodeficiency with 'healthy' children on measures of social competence and executive functioning. This 'healthy' group were employed to control for factors such as IQ and key socio-demographic variables and as such was important in addressing the research questions. Many of the previous studies that have investigated psychological outcome for BMT survivors have not used a control group and hence this represents an improvement in methodological quality. However, the question is raised, is it really fair to compare children who have experienced a life threatening illness and undergone extensive medical treatment to children with absolutely no history of chronic illness? Given the huge disruption to both the child's development and to family functioning that BMT engenders is it really surprising that a



number are encountering more difficulties with regard to social functioning? By using traditional measures of assessment and comparing these children to healthy peers are we in fact pathologising normal reactions to a very abnormal event (i.e. BMT). In addition, data obtained through self report measures such as those used in the current study are further limited, given that the parent of a child who has survived a chronic illness will likely be using a different 'baseline' compared to a parent of a 'healthy' child. If we really want to determine whether a particular group of chronically ill children are experiencing psychological difficulties then perhaps we should compare them to children who have also faced a life threatening disease and have undergone similar treatment. This is a more time consuming method and was outside the scope of the current thesis, however, it may have provided more ecologically valid results.

*A bias towards significant findings...*

It has long been suggested that there are likely to be a relatively large number of unpublished studies that have less significant results than the published studies (Rosenthal, 1979). This is referred to as 'publication bias' with evidence to suggest that the bias is real (Sterling et al., 1995). One would like to think that in research with chronically ill populations a non-significant finding, representing the absence of the hypothesised difficulties, is as much a valid and scientifically interesting finding as results demonstrating significant difficulties. However, given this tendency towards significant findings, consideration must be given to the idea that we may be overestimating the difficulties experienced by children treated with BMT. Indeed, a number of children are doing extremely well, with IQ scores within the superior range and no problems with psychosocial functioning. Perhaps it might be useful to shift the emphasis away from a psychopathological approach to focus more on resilience factors and the coping styles that

enable some children to develop apparently unscathed by their history of illness and treatment.

Revisiting the concept of a publication bias, it likely lies as much with the authors as with the journal editors. When investing large amounts of time and often money into research, it is natural to want to find something interesting, that is, something *significantly* interesting. Perhaps so much so that one either consciously or unconsciously influences the results in favour of their hypotheses. One of major limitations of the current thesis, is that there was only one experimenter, me. I was therefore obviously fully aware of the hypotheses and was eager to conduct a piece of research that would make a significant contribution to the evidence base. Being aware of this potential 'experimenter bias', at all stages of the research, was essential in ensuring that it did not influence the study. I was careful to conduct the research in the same rigorous way with both the clinical and control group, ensuring that the same instructions were given and that the same testing procedures were carried out. I was also keen to ensure that I was scoring the tests in the same way and so enlisted the help of a colleague who was blind to the study hypotheses to re-score a subset of cognitive tests that required some judgements to be made. Whilst I am confident that I did not influence the results obtained in any way, using a different experimenter who was blind to the study hypotheses to collect the data would have improved the methodological quality of the research.

### **What next? Theoretical and clinical implications of the current thesis**

The next question is what to do with this information gained through research. With regard to children treated with BMT for congenital immunodeficiency, I believe that we are now at the stage of starting to develop a theoretical framework to describe, explain and predict how children's psychological (cognitive and psychosocial) adjustment is influenced by the BMT process and to guide intervention. The evidence to date suggests that this cohort of

long term survivors of paediatric BMT demonstrate considerable individual variability with regard to psychological functioning post transplant. In addition, where difficulties are identified, they are rarely isolated and discreet. Children can present with different types of cognitive problems and emotional, social and behavioural problems. It is therefore likely that psychological adjustment post BMT is one of the many fields that need a broad theoretical base incorporating frameworks, theories and models from a number of different areas. In order to develop such an all-encompassing theoretical framework, it is useful to draw from established models used in other areas of clinical research. I have used the structure of a model developed by Barbara Wilson (2002) for use when assessing and providing interventions for people with brain injury. Like children treated with BMT for congenital immunodeficiency, patients with brain injury often present with complex difficulties comprising cognitive, social, emotional and behavioural problems. This model, adapted for children treated with BMT for congenital immunodeficiency is presented in figure 1, (p 118).

The model starts with the child and family. Pre BMT cognitive and psychosocial functioning and family functioning have all been found to influence long term outcome. In addition, social and demographic factors, including socio economic status and parental consanguinity have been identified as predictors of cognitive and psychosocial functioning in this cohort of children post BMT. Furthermore, it is likely that child personality and temperament factors and the nature of parent child attachment will affect post BMT psychological adjustment, although research has yet to be conducted in these areas. Consequently it is important to carry out pre BMT assessments and to collect socio-demographic information.

The nature and severity of the immune condition needs to be determined from medical assessments. Evidence suggests that certain subgroups of children with congenital immunodeficiency are at increased risk of developing cognitive and psychosocial

difficulties, in particular children treated for ADA SCID and Chediak Higashi syndrome. In addition, the evidence to date suggests differences in outcome between children whose condition is confined to their immune system and those whose condition is expressed systemically. This information together with data collected in the pre-BMT assessments could be used to predict which children might be most at risk for post transplant psychological difficulties. At this stage, models of psycho-education may be important. Families are likely to need information regarding possible medical and psychological outcomes in addition to education concerning terminology and medical procedures.

Identification of problems is one of the most important tasks necessary for effective intervention. This is really where good quality empirical research comes into play. Survivors beyond a couple of years post BMT typically return infrequently to Great Ormond Street Hospital. Hence contact with the long term survivor population is maintained primarily through research and for monitoring their health. Thus far, this research has been instrumental in bringing to our attention, issues that we might otherwise have been unaware of. In terms of the assessment of difficulties, it is likely that one would need to draw upon several theoretical frameworks, including the use of neuropsychological tests; information from functional or behavioural assessments and qualitative information gained through clinical interviews. This information can be used to build up a profile of strengths and weaknesses and to develop an understanding of how the problems affect everyday life.

Once problems have been identified, intervention strategies can be implemented. This would firstly involve the negotiation of goals with the child, family and other professionals involved in the system of care, such as teachers and health professionals. Again, depending upon the difficulties identified, intervention would likely be based upon any number of theoretical frameworks. For example, if cognitive difficulties were targeted for intervention, this may involve drawing upon models of cognitive rehabilitation, such as models of

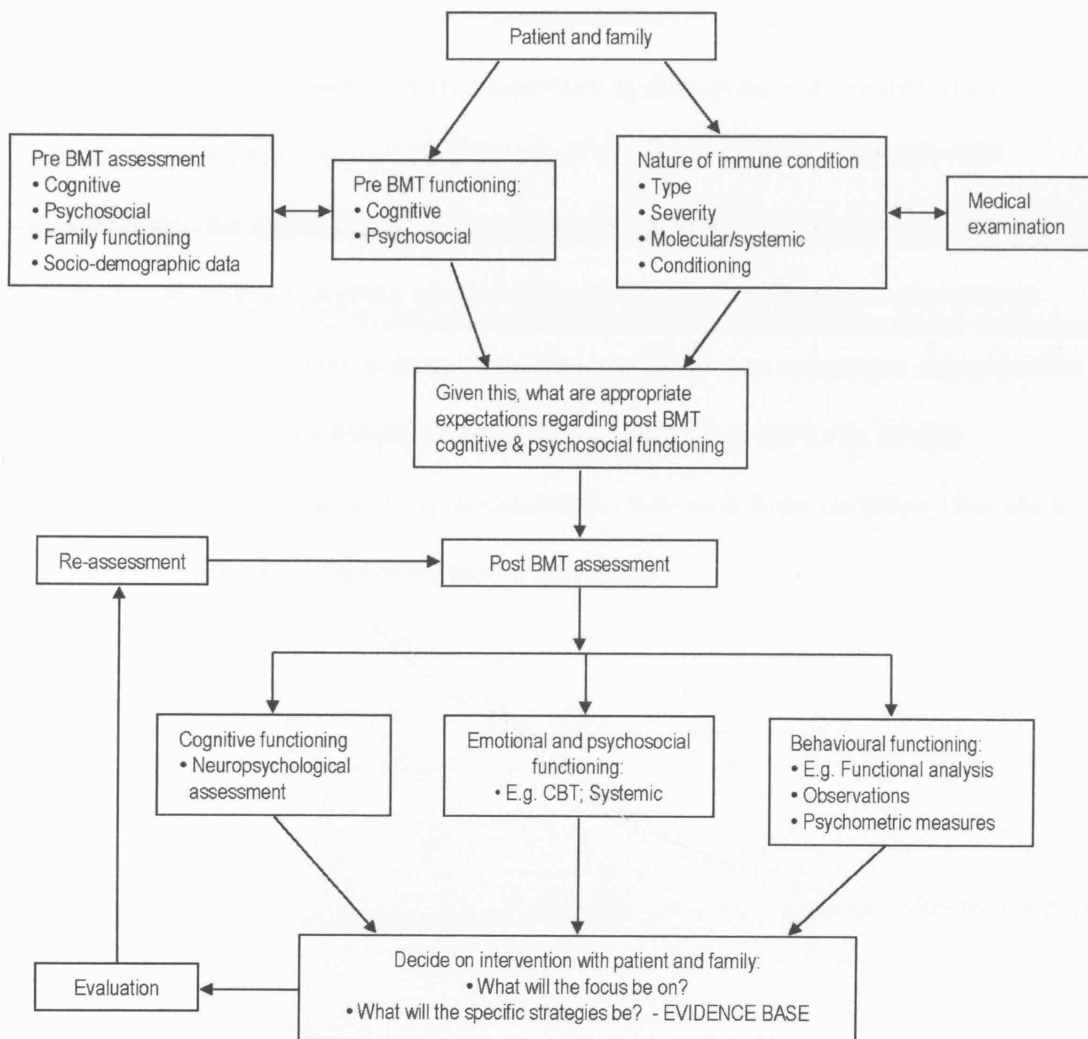
memory (e.g. Baddely, 1992), language (e.g. Coltheart, 1985) and attention (e.g. Posner, 1980) to name but a few. Alternatively, emotional difficulties may be the focus of intervention with models such as Cognitive Behavioural Therapy (e.g. Beck, 1996) being used. Perhaps, however, the main difficulties may concern family relationships following the disruption to these caused by the transplant process. Systemic theories might then be used to guide assessment and intervention (see Hayes, 1991 for a review). Furthermore, behavioural difficulties may be identified as the main target for intervention. In this case, behavioural models such as those originally proposed by Skinner (1938, 1953) would be instrumental in understanding the function of the behaviour and intervening to produce a change in behaviour.

The final question concerns how to evaluate outcome following intervention. Ideally measures should be devised that are specific to the needs of this particular population of children and that measure outcome in relation to the goals set.

The development of such a theoretical framework, would, at this stage, provide scaffolding from which to continue to build. Relatively little research has been carried out with this particular population of children and there are numerous areas to explore. However, since difficulties post BMT have been identified, it is important to start exploring interventions for these children and their families. This is not as straightforward as the suggested model would seem to propose. The major limitation is that these long term survivors are spread throughout England and Wales and so are unable to attend Great Ormond Street Hospital on a regular basis. They are therefore reliant upon local services that are unlikely to fully understand the complex nature of the difficulties experienced by these children. In developing a theoretical framework to guide assessment and intervention, it may be necessary to forge closer links with the child's local services and in essence provide consultation to professionals working with the child on a regular basis. In developing

interventions for children experiencing difficulties, it may also be important to use other means such as internet based intervention programmes that could be monitored centrally at Great Ormond Street Hospital.

Figure 1: *Suggested theoretical framework (Adapted from Wilson., 2001)*



To conclude, research has only recently begun to investigate the long term psychological outcome for children treated with BMT for Congenital Immunodeficiencies. As such opportunities for research combining theory, scientific methodology and clinical relevance are plentiful. Given the established variability in this cohort of children in terms of outcome, future research would benefit from focussing not only on identifying and seeking to explain difficulties but also on examining the mechanisms and pathways that support positive outcomes. Furthermore, there are exciting opportunities for empirical research with regard to developing interventions for children experiencing difficulties. The children treated for congenital immunodeficiency are possibly one of the only cohorts of paediatric BMT survivors where the improvement in methodological quality, through the work conducted by Titman et al. (in press) and the current study, give some solid findings from which to begin to explore intervention strategies. This is currently an area completely unexplored in this population of children and given that groups of children at risk for or already experiencing, later cognitive and psychosocial difficulties have been identified, clinically it would seem important to start to focus on intervention.

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## **Appendix 1**

Child and parent information sheets – congenital  
immunodeficiency group

**Information sheet for children & young people (8-16)**

**Social functioning in children treated with bone marrow transplant (BMT)  
for an immune disorder.**

You are being invited to take part in a research study. Before you decide whether you would like to take part or not it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

**What is the purpose of this study?**

We have carried out some tests with children and young people who have been treated with bone marrow transplant for an immune disorder at Great Ormond Street Hospital. You may have taken part in these tests. The results from this study helped us to understand the effects of an immune disorder on children and their families. Some of our findings were especially interesting and we would now like to carry out more tests to understand them even better. These tests involve puzzles, some computer games and answering some questions. Most children and young people enjoy doing them.

**Why have I been chosen?**

You have been chosen because you have had a bone marrow transplant for an immune disorder and are between the ages of 8-16 years old.

**Do I have to take part?**

It is up to you to decide whether or not you want to take part. If you decide to take part you will be given this information sheet to keep and will be asked to sign a consent form. If you decide to take part you are still free to withdraw at any time and without giving a reason.

**What will happen if I agree to take part?**

We will arrange a time with you to come and do the tests. This can be at the hospital or at your home if you'd prefer. The tests will involve you doing some puzzles, computer games and answering some questions. You will also be asked to fill in one or two short questionnaires. The tests should take no longer than 1½ hours to complete. At the end of the study you will be sent a report of the findings from the project for you to keep.

**What are the possible disadvantages and risks of taking part?**

There are no risks involved in taking part in the study. If during the tests we find any difficulties or if you have any concerns we can arrange to talk with you about these in more detail and give advice about how to get further help from your local services.

**What are the possible benefits of taking part?**

We hope that this study will help us to understand even better the long-term outcome for children who have had an immune disorder. This will help us to become better at supporting children and their families who have had or are going to have treatment for this condition.

**What will happen to the results of the research study?**

The information will be kept secretly on a computer and will be analysed with some of the information we have already collected. These results will be presented at conferences and may be published in medical journals.

**Who do I speak to if problems happen?**

If you have any worries about the way this research project has been or is being done, please first speak to the researcher. If the problems are not sorted out or you wish to comment in any other way, please contact Emma Pendelton by post via the Research and Development Office, Institute of Child Health, 30 Guildford Street, London, WC1N 1EH or if urgent by telephone on 020 7905 2179.

**Researchers who will have contact with you and contact details:**

Emily Skucek, Trainee Clinical Psychologist  
Great Ormond Street Hospital,  
London,  
WC1N 3JH  
Tel: 020 7829 8679 or 0207 405 9200 ext 0546

Dr Penny Titman, Consultant Clinical Psychologist  
Great Ormond Street Hospital,  
London,  
WC1N 3JH  
Tel: 020 7829 8679 or 0207 405 9200 ext 0546

Iain Edgley, Assistant Psychologist  
Great Ormond Street Hospital,  
London,  
WC1N 3JH  
Tel: 020 7829 8679 or 0207 405 9200 ext 0546

**Thank you for taking the time to read this**

VERSION 2; DATE 23/03/2007

**Information sheet for Parent(s)/Guardian(s)**

**Social functioning in children treated with bone marrow transplant (BMT) for an immune disorder.**

**Dear Parent(s)/Guardian(s),**

You are being invited to give consent for your child to take part in a research study. Before you decide whether you would like your child to participate or not it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish your child to take part.

**What is the purpose of this study?**

We have carried out psychological assessments with children and young people who have been treated with bone marrow transplant for an immune disorder at Great Ormond Street Hospital. Your child \_\_\_\_\_ was included as part of that study. The results from this study have helped us to understand the long-term impact of immunodeficiency on children and their families. Some of our findings were especially interesting and we would now like to carry out more tests to understand them even better. This will involve your child completing a few tests involving memory, attention and planning, some computer based tests and answering some questions. Most children and young people enjoy doing them.

**Why have I been chosen?**

All families of children, aged 8-16 years, with a diagnosis of Severe Combined Immunodeficiency (SCID), Combined Immunodeficiency (CID) and Wiskott Aldrich Syndrome who have taken part in the long term follow up study have been approached to take part in this study.

**Does my child have to take part?**

It is up to you to decide whether or not you want your child to take part. If you do decide they can take part you will be given this information sheet to keep and will be asked to sign a consent form. If you decide they can take part you are still free to withdraw them at any time and without giving a reason.

**What will happen if I agree to take part?**

We will arrange a convenient time with you and your child to do the assessment. This can be at the hospital or at your home if you'd prefer. The assessment will involve testing your child's memory and attention, then completing some computer based tests and answering some questions. He/she will also be asked to fill in one or two short questionnaires. You will be asked to complete 3 brief questionnaires about your child. With your permission we will also ask your child's teacher to complete 2 brief questionnaires about your child. The whole assessment should take no longer than 1½ hours to complete. At the end of the study, you will be sent a report of the findings from the project for you to keep.

**What are the possible disadvantages and risks of taking part?**

There are no risks involved in taking part in the study. If during the tests we find any difficulties or if you have any concerns about your child's learning or behaviour, we can arrange to discuss these with you about these in more detail and provide advice about how to seek further support for these from your local services.

**What are the possible benefits of taking part?**

We hope that this study will help us to understand even better the long-term outcome for children who have had an immune disorder. This will help us to become better at supporting children and their families who have had or are going to have treatment for this condition.

**What will happen to the results of the research study?**

The information will be stored anonymously on a computer database and will be analysed with some of the information we have already collected. These results will be analysed and presented at conferences and may be published in medical journals.

**Who do I speak to if problems happen?**

If you have any complaints about the way this research project has been or is being conducted, please, in the first instance discuss them with the researcher. If the problems are not resolved or you wish to comment in any other way, please contact Emma Pendelton by post via the Research and Development Office, Institute of Child Health, 30 Guildford Street, London, WC1N 1EH or if urgent by telephone on 020 7905 2179.

**Researchers who will have contact with you and contact details:**

Emily Skucek, Trainee Clinical Psychologist  
Great Ormond Street Hospital,  
London,  
WC1N 3JH  
Tel: 020 7829 8679 or 0207 405 9200 ext 0546

Dr Penny Titman, Consultant Clinical Psychologist  
Great Ormond Street Hospital,  
London,  
WC1N 3JH  
Tel: 020 7829 8679 or 0207 405 9200 ext 0546

Iain Edgley, Assistant Psychologist  
Great Ormond Street Hospital,  
London,  
WC1N 3JH  
Tel: 020 7829 8679 or 0207 405 9200 ext 0546

**Thank you for taking the time to read this**

VERSION 2; DATE 23/03/2007

## **Appendix 2**

### Consent forms



# Great Ormond Street Hospital for Children



NHS Trust

Great Ormond Street  
London WC1N 3JH

Tel: 020 7405 9200

Great Ormond Street Hospital for Children NHS Trust and Institute of Child Health  
Research Ethics Committee

## Consent Form for CHILDREN & YOUNG PEOPLE (8-16years) Participating in Research Studies

**Title: Social functioning in children treated with bone marrow transplant (BMT) for Congenital immunodeficiency**

### NOTES FOR CHILDREN & YOUNG PEOPLE

1. You have been asked to take part in a research study. The person organising that study must explain the project to you before you agree to take part.
2. Please ask the researcher any questions you like about this project, before you decide whether to join in.
3. If you decide, now or at any other time, that you do not wish to be involved in the research project, just tell us and we will stop the research. If you are a patient your treatment will carry on as it would normally.
4. You will be given an information sheet, which describes the research. This information sheet is for you to keep and look at any time. **Please read it carefully.**
5. If you have any complaints about the research project, discuss them with the researcher. If the problems are not sorted out, or you wish to comment in any other way, please contact Emma Pendelton via the Research and Development Office, Institute of Child Health, 30 Guildford Street, London WC1N 3EH, Tel no 020 7905 2179.

### CONSENT

I \_\_\_\_\_ agree that the Research Project named above has been explained to me to my satisfaction, and I agree to take part in this study. I have read both the notes written above and the Information Sheet provided, and understand what the research study involves.

**SIGNED**

**PRINTED**

**DATE**

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**SIGNED (Researcher)**

**PRINTED**

**DATE**

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In Partnership with the Institute of Child Health, UCL  
Patron: Her Majesty The Queen  
Chairman: Sir Cyril Chantler MA MD FRCP FRCPCH FMedSci



Great Ormond Street  
Hospital for Children



NHS Trust

Great Ormond Street  
London WC1N 3JH

Tel: 020 7405 9200

Great Ormond Street Hospital for Children NHS Trust and Institute of Child Health  
Research Ethics Committee

**Consent Form for PARENTS OR GUARDIANS of Children Participating in  
Research Studies**

**Title: Social functioning in children treated with bone marrow transplant  
(BMT) for Congenital immunodeficiency**

**NOTES FOR PARENTS OR GUARDIANS**

1. Your child has been asked to take part in a research study. The person organising that study is responsible for explaining the project to you before you give consent.
2. Please ask the researcher any questions you may have about this project, before you decide whether you wish to participate.
3. If you decide, now or at any other stage, that you do not wish your child to participate in the research project, that is entirely your right, and if your child is a patient it will not in any way prejudice any present or future treatment.
4. You will be given an information sheet, which describes the research project. This information sheet is for you to keep and refer to. **Please read it carefully.**
5. If you have any complaints about the way in which this research project has been or is being conducted, please, in the first instance, discuss them with the researcher. If the problems are not resolved, or you wish to comment in any other way, please contact Emma Pendelton via the Research and Development Office, Institute of Child Health, 30 Guildford Street, London WC1N 3EH, Tel no 020 7905 2179.

**CONSENT**

I/We \_\_\_\_\_, being the parent(s)/guardian(s) of

NAME: \_\_\_\_\_ DATE OF BIRTH: \_\_\_\_\_ Agree that the Research Project named above has been explained to me to my/our satisfaction, and I/We give permission for our child to take part in this study. I/We have read both the notes written above and the Information Sheet provided, and understand what the research study involves.

\*

**SIGNED (Parent(s)/Guardian(s))**

**PRINTED**

**DATE**

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**SIGNED (Researcher)**

**PRINTED**

**DATE**

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\* VERSION 1; DATE 09/02/2007



WWG001

In Partnership with the Institute of Child Health, UCL  
Patron: Her Majesty The Queen  
Chairman: Sir Cyril Chantler MA MD FRCP FRCPCH FMedSci



## **Appendix 3**

Child and parent information sheets – control group



### **Information sheet for children & young people (8-16)**

#### **Social functioning in children treated with bone marrow transplant (BMT) for an immune disorder.**

You are being invited to take part in a research study. Before you decide whether you would like to take part or not it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

#### **What is the purpose of this study?**

We have carried out some tests with children and young people who have been treated with bone marrow transplant for an immune disorder at Great Ormond Street Hospital. The results from this study helped us to understand the effects of an immune disorder on children and their families. Some of our findings were especially interesting and we would now like to carry out more tests to understand them even better. We would like to compare these results with those of healthy children, like you, who are similar in terms of age, gender, ethnicity and intelligence to the patient children, but who have not had an immune disorder. These tests involve puzzles, some computer games and answering some questions. Most children and young people enjoy doing them.

#### **Why have I been chosen?**

You have been chosen because you are a healthy child/young person with no history of long-term illness and are between the ages of 8-16 years old.

#### **Do I have to take part?**

It is up to you to decide whether or not you want to take part. If you decide to take part you will be given this information sheet to keep and will be asked to sign a consent form. If you decide to take part you are still free to withdraw at any time and without giving a reason.

#### **What will happen if I agree to take part?**

We will arrange a time with you and your school to come and do the tests in a quiet room at your school. The tests will involve you doing some puzzles, computer games and answering some questions. You will also be asked to fill in one or two short questionnaires. Because we want healthy children to match patient children for intelligence some of you will be given a few brief tests and others will be asked to complete more. The tests should take no longer than 1½ hours to complete. With this sort of study we may find that we have enough information before you get to take part and so not everyone who agrees to join in will actually be tested. At the end of the study, if you have taken part, you will be sent a report of the findings from the project for you to keep.

**What are the possible disadvantages and risks of taking part?**

There are no risks involved in taking part in the study. If during the tests we find any difficulties or if you have any concerns we can arrange to talk with you about these in more detail and give advice about how to get further help from your local services.

**What are the possible benefits of taking part?**

If you agree to take part in the study you will be entered into a raffle at your school. The prize for the winner, drawn at random, will be £40 worth of HMV vouchers. Also, We hope that this study will help us to understand even better the long-term outcome for children who have had an immune disorder. This will help us to become better at supporting children and their families who have had or are going to have treatment for this condition.

**What will happen to the results of the research study?**

The information will be kept secretly on a computer and will be analysed with some of the information we have already collected. These results will be presented at conferences and may be published in medical journals.

**Who do I speak to if problems happen?**

If you have any worries about the way this research project has been or is being done, please first speak to the researcher. If the problems are not sorted out or you wish to comment in any other way, please contact Emma Pendelton by post via the Research and Development Office, Institute of Child Health, 30 Guildford Street, London, WC1N 1EH or if urgent by telephone on 020 7905 2179.

**Researchers who will have contact with you and contact details:**

Emily Skucek, Trainee Clinical Psychologist

Dr Penny Titman, Consultant Clinical Psychologist

Iain Edgley, Assistant Psychologist

**Thank you for taking the time to read this**

VERSION 2; DATE 23/03/2007

**Information sheet for Parent(s)/Guardian(s)**

**Social functioning in children treated with bone marrow transplant (BMT) for an immune disorder.**

**Dear Parent(s)/Guardian(s),**

You are being invited to give consent for your child to take part in a research study. Before you decide whether you would like your child to participate or not it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish your child to take part.

**What is the purpose of this study?**

We have carried out psychological assessments with children and young people who have been treated with bone marrow transplant for an immune disorder at Great Ormond Street Hospital. The results from this study have helped us to understand the long-term impact of immune disorder on children and their families. Some of our findings were especially interesting and we would now like to carry out more tests to understand them even better. In order for us to tell whether our findings are specific to this group of children we would like to compare their results with those of healthy children/young people. We are looking to match the patient children with healthy, non-chronically ill children in terms of age, gender, ethnicity and intelligence. This will involve your child completing some puzzles, some computer games and answering some questions. Most children and young people enjoy doing them.

**Why has my child been chosen?**

Families of healthy children, aged 8-16 years, who attend \_\_\_\_\_  
\_\_\_\_\_ school are being approached to take part in this study.

**Does my child have to take part?**

It is up to you to decide whether or not you want your child to take part. If you do decide they can take part you will be given this information sheet to keep and will be asked to sign a consent form. If you decide they can take part you are still free to withdraw them at any time and without giving a reason.

**What will happen if I agree for my child to take part?**

We will arrange a convenient time with your child and their teacher to do the assessment, in a quiet room at their school. Because we want to match healthy children with control children for intelligence, all children whose parents have consented for them to take part will be given a brief assessment, taking no more than 20 minutes to complete. This will involve them doing some puzzles and answering some questions. This is sometimes called a cognitive assessment or an IQ test. Those children who match the patient children on this variable will be asked to complete further tests. These include more puzzles and questions and also some computer games. He/she will also be asked to fill in one or two short questionnaires. If your child is asked to complete the full assessment, you will be asked to complete 3 brief questionnaires about your child. With your permission we will also ask your child's teacher to complete 4 brief questionnaires about your child. The full assessment should take no longer than 1 ½ hours to complete. With this sort of study we may find that we have enough information before your child gets to take part. Therefore not every child who consents to the study will actually be asked to take part. At the end of the study, if you have taken part, you will be sent a report of the findings from the project for you to keep.

**What are the possible disadvantages and risks of taking part?**

There are no risks involved in taking part in the study. If during the tests we find any difficulties or if you have any concerns about your child's learning or behaviour, we can arrange to discuss these with you about these in more detail and provide advice about how to seek further support for these from your local services.

**What are the possible benefits of taking part?**

If your child has consented to take part in the study, they will be entered into a raffle, which will take place at their school. The prize for the winner, drawn at random, will be £40 worth of HMV vouchers. In addition, we hope that this study will help us to understand even better the long-term outcome for children who have had an immune disorder. This will help us to become better at supporting children and their families who have had or are going to have treatment for this condition.

**What will happen to the results of the research study?**

The information will be stored anonymously on a computer database and will be analysed with some of the information we have already collected. These results will be analysed and presented at conferences and may be published in medical journals.

**Who do I speak to if problems happen?**

If you have any complaints about the way this research project has been or is being conducted, please, in the first instance discuss them with the researcher. If the problems are not resolved or you wish to comment in any other way, please contact Emma Pendelton by post via the Research and Development Office, Institute of Child Health, 30 Guildford Street, London, WC1N 1EH or if urgent by telephone on 020 7905 2179.

**Researchers who will have contact with you and contact details:**

Emily Skucek, Trainee Clinical Psychologist

Dr Penny Titman, Consultant Clinical Psychologist

Iain Edgley, Assistant Psychologist

**Thank you for taking the time to read this**

VERSION 2; DATE 23.03.07

## **Appendix 4**

### Demographic information sheet



## Demographic Information Sheet

Child's name:

Please state the above named child's ethnicity:

Is English the above named child's first language?      Yes / No

If no, please state the above named child's first language:

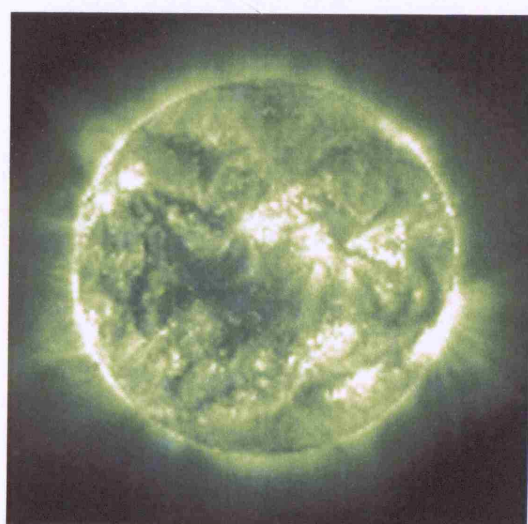
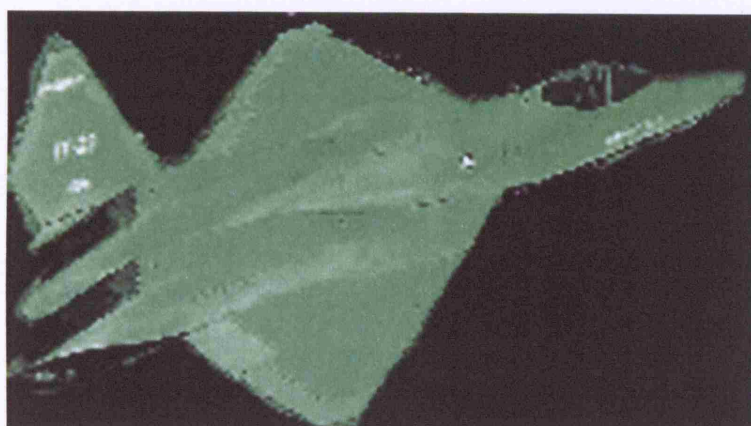
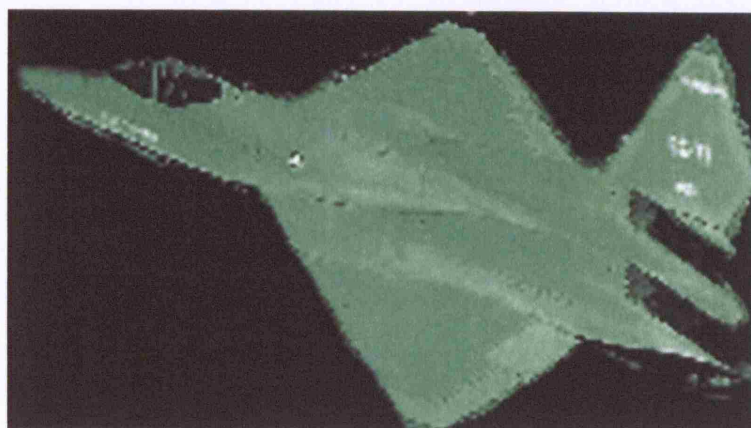
Please state the occupation of the above named child's father:

Please state the occupation of the above named child's mother:

Are the above named child's parents related? (e.g. cousins etc)

## **Appendix 5**

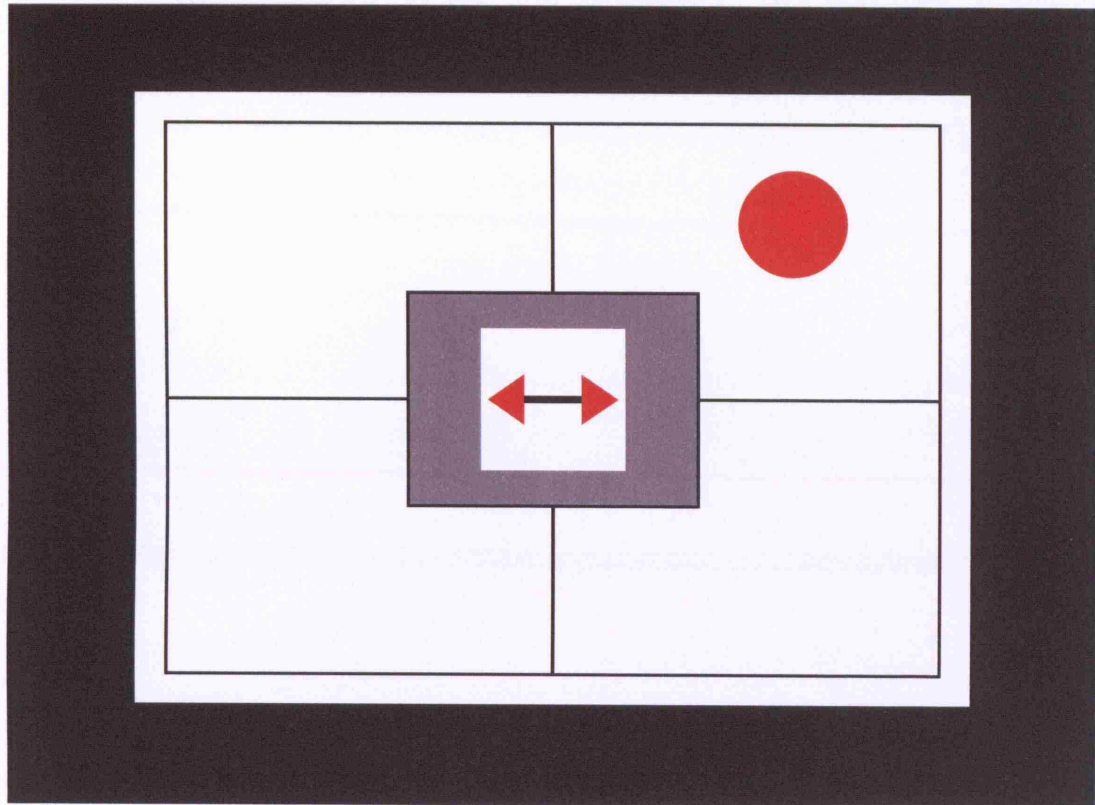
Illustration of 'Go-No-Go' task stimuli



## **Appendix 6**

Illustration of 'Switch' task stimuli

## Appendix 7

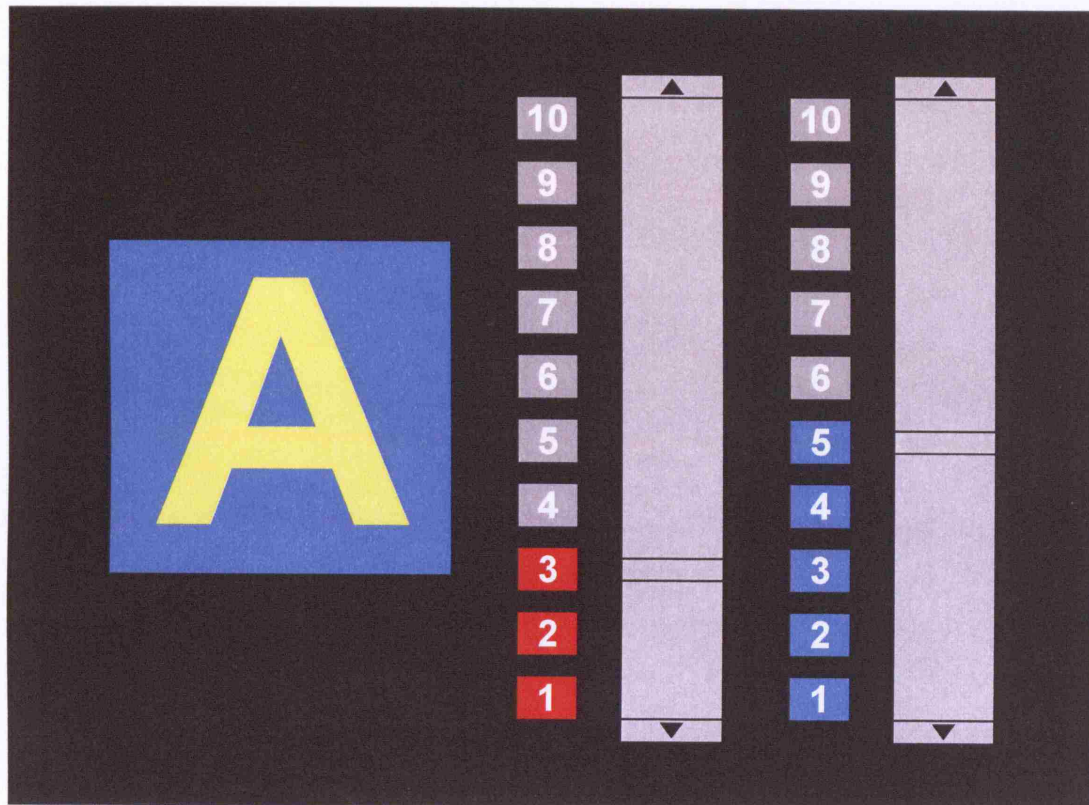


## **Appendix 7**

Illustration of 'Reward CPT' task stimuli

## Appendix A

### Figure A-1.2.3.1: 10-Step



## **Appendix 8**

Ethical approval letter





## National Research Ethics Service

Institute of Child Health/Great Ormond Street Hospital Research Ethics Committee

The Institute of Child Health  
30 Guilford Street  
London  
WC1N 1EH

Telephone: 020 7905 2620  
Facsimile: 020 7905 2201

17 April 2007

Miss Emily Skucek  
Trainee Clinical Psychologist  
Great Ormond Street Hospital NHS Trust  
Great Ormond Street  
London WC1N 3JH

Dear Miss Skucek

**Full title of study:** Social Functioning in Children treated with Bone Marrow Transplant (BMT) for Congenital Immunodeficiency  
**REC reference number:** 07/Q0508/10

Thank you for your letter of 23 March 2007, responding to the Committee's request for further information on the above research and submitting revised documentation.

The further information has been considered on behalf of the Committee by the Chairman.

### Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised.

### Ethical review of research sites

The favourable opinion applies to the research sites listed on the attached form.

### Conditions of approval

The favourable opinion is given provided that you comply with the conditions set out in the attached document. You are advised to study the conditions carefully.

### Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document	Version	Date
Application		16 February 2007
Investigator CV	for Emily Skucek	09 February 2007
Protocol	1	09 February 2007
Covering Letter		16 February 2007
Peer Review	Chris Barker	13 November 2006
Compensation Arrangements		01 August 2006
Questionnaire: Matson Evaluation of Social Skills with Youngsters		
Questionnaire: Standardised Questionnaires, Vineland Adaptive		

This Research Ethics Committee is an advisory committee to London Strategic Health Authority  
The National Research Ethics Service (NRES) represents the NRES Directorate within  
the National Patient Safety Agency and Research Ethics Committees in England

Behavior Scales		
Questionnaire: Strengths and Difficulties Questionnaire		
Questionnaire: Teacher's Rating Scale of Child's Actual Behaviour		
Questionnaire: Self perception profile for children, "What I Am Like"		
Participant Information Sheet: Children/ Young People, 8 - 16 (control)	1	09 February 2007
Participant Information Sheet: Parent/ Guardian (control group)	1	09 February 2007
Participant Information Sheet: Children and Young Person, 8 - 16 (Clinical Group)	1	09 February 2007
Participant Information Sheet: Parent/ Guardian (Clinical Group)	1	09 February 2007
Participant Information Sheet: Parent/ Guardian, Clinical Group	2	23 March 2007
Participant Information Sheet: Information Sheet, 8-16, Clinical Group	2	23 March 2007
Participant Information Sheet: Parent Information Sheet - Control Group	2	23 March 2007
Participant Consent Form: Children & Young People, 8 - 16	1	09 February 2007
Participant Consent Form: Parent/ Guardian	1	09 February 2007
Response to Request for Further Information		23 March 2007
Letter from Llantwit Major School		25 January 2007
CV of Dr Penny Titman		09 February 2007
Supervisor CV	Dr Pasco Fearon	09 February 2007

#### R&D approval

The study should not commence at any NHS site until the local Principal Investigator has obtained final approval from the R&D office for the relevant NHS care organisation.

#### Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees (July 2001) and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

<b>07/Q0508/10</b>	<b>Please quote this number on all correspondence</b>
--------------------	---

With the Committee's best wishes for the success of this project

Enclosures: Standard approval conditions: SL-AC2 for studies other than Clinical Trials of Investigational Medicinal Products  
Site approval form

Copy to: Great Ormond Street Hospital NHS Trust/ Institute of Child Health  
R&D Department

An advisory committee to London Strategic Health Authority

Institute of Child Health/Great Ormond Street Hospital Research Ethics Committee				
LIST OF SITES WITH A FAVOURABLE ETHICAL OPINION				
For all studies requiring site-specific assessment, this form is issued by the main REC to the Chief Investigator and sponsor with the favourable opinion letter and following subsequent notifications from site assessors. For issue 2 onwards, all sites with a favourable opinion are listed, adding the new sites approved.				
REC reference number:	07/Q0508/10	Issue number:	0	Date of issue: 17 April 2007
Chief Investigator:	Miss Emily Skucek			
Full title of study:	Social Functioning in Children treated with Bone Marrow Transplant (BMT) for Congenital Immunodeficiency			
This study was given a favourable ethical opinion by Institute of Child Health/Great Ormond Street Hospital Research Ethics Committee on 04 April 2007. The favourable opinion is extended to each of the sites listed below. The research may commence at each NHS site when management approval from the relevant NHS care organisation has been confirmed.				
Principal Investigator	Post	Research site	Site assessor	Date of favourable opinion for this site
Miss Emily Skucek	Honorary Trainee Clinical Psychologist (pending)	Great Ormond Street Hospital	Institute of Child Health/Great Ormond Street Hospital Research Ethics Committee	17/04/2007
Notes <sup>(1)</sup>				

(1) The notes column may be used by the main REC to record the early closure or withdrawal of a site (where notified by the Chief Investigator or sponsor), the suspension of termination of the favourable opinion for an individual site, or any other relevant development. The date should be recorded.

